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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1954

ORIGINAL ARTICLES

COMPOUNDS E AND F, AND ACTH IN THE MANAGEMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA*

By Chris J. D. Zarafonetis, M.D.
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William A. Steiger, M.D.
Associate in Medicine
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Few clinical entities are as capricious and treacherous as idiopathic thrombocytopenic purpura[6]. Despite newer knowledge with reference to autoimmune mechanisms[4,5,9], its etiology remains obscure. While some subjects undergo spontaneous remission, the course of a given patient with idiopathic thrombocytopenic purpura still cannot be predicted with assurance. For this reason, proper diagnosis and appropriate therapy are of paramount importance. During recent years, the use of cortisone has been found to be of considerable value in the treatment of purpura[2,3,7,8,10,11]. The present study was undertaken in an attempt to delineate the therapeutic role of cortisone and adrenocorticotrophic hormone (ACTH) in this disorder. Later the study was extended to include an evaluation of Compound F when this compound also became available.†

The observations to be reported herein, therefore, are primarily relevant to the problem of therapy of idiopathic thrombocytyopenic purpura. In addition, however, attention will be drawn to the value of the treponema immobilization test on sera from cases with positive serologic tests for syphilis[1].

Material and Methods. Eleven patients with idiopathic thrombocytopenic purpura form the basis of this study. Complete history and physical examination were routinely performed in each case. No evidence was obtained that allergic, drug or other reaction was a factor in any of these subjects.

Studies included the Rumpel-Leede test for capillary fragility. The pressure of the sphygmomanometer was held at 10 mm. Hg above the patient's diastolic pressure for 5 minutes. Counts were made of the petechiae

*This study was aided by the Temple University Medical School Hematology Research Fund.

†The authors wish to thank Merck & Co., Rahway, N. J. for generously providing the Compound F (Hydrocortone) used in this study.

appearing in a circle 2.5 cm. in diameter, at a point just below the antecubital fossa. The results were scored 4+ if too numerous to count; 3+ if more than 50 petechiae; 2+ if 20 to 50, and 1+ if less than 20, but more than 4. Less than 4 petechiae was considered negative. Bleeding-time (Duke) and clotting time (Lee-White) were performed as part of the base-line work-up, as was bone-marrow aspiration. Direct Coombs' tests on the patients' cells and tests for L.E. cells (lupus erythematosus) were also done. The platelet counts were performed by a method adapted from that of Osgood and Wilhelm for counting reticulocytes. This technique has been employed in this laboratory for several years and the normal range of platelets for the method is 200,000 to 500,000 per c.mm. Serologic tests for syphilis were routinely performed.

During the period of therapy with Compound F or E, or ACTH, the patients were on a low sodium diet and received supplements of potassium citrate. Compound F was administered orally except in Case 4, where the initial trial of this substance was conducted using parenteral injection for comparative purposes. Cases 1 and 4 received parenteral Compound E on one occasion each. ACTH was given parenterally during the operative period in 3 of 4 patients undergoing splenectomy, in order to stimulate adrenal cortical function and nullify the suppressive effect of previous Compound F or E therapy. In 2 cases with partial platelet response to oral Compound F medication, courses of ACTH therapy were also undertaken. Two additional subjects received small doses of ACTH at the termination of courses of oral steroid therapy.

Brief case histories giving the results of therapy in these patients follow.

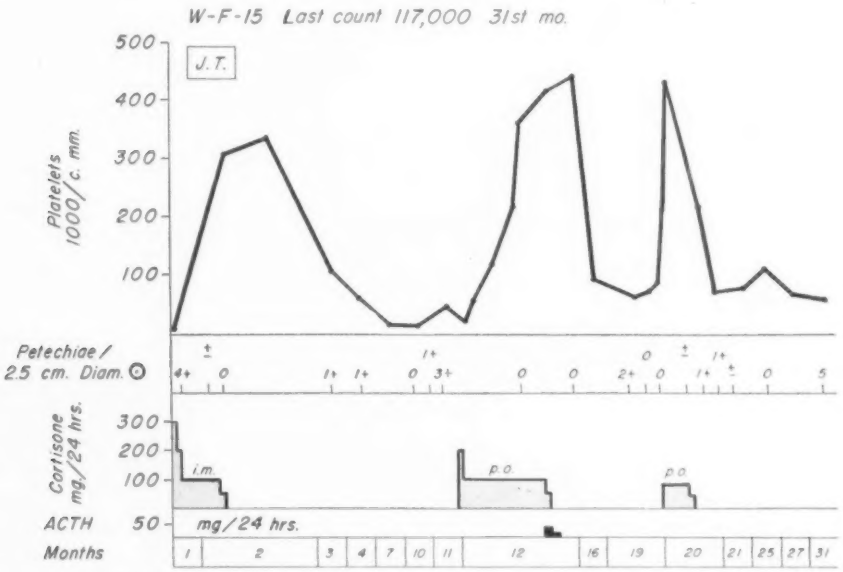

Fig. 1.—Patient J. T. Platelet counts and capillary fragility in idiopathic thrombocytopenic purpura during and after 3 courses of cortisone therapy. (Note compression of time scale in this and subsequent charts.)

Case Reports. CASE 1 (Fig. 1) J. T., a 15-year-old white schoolgirl was admitted to Temple University Hospital on April 25, 1951, because of profuse vaginal bleeding. She had been treated elsewhere by packing and by dilatation and curettage, but bleeding recurred and blood transfusions were necessitated. One week prior to her transfer to this hospital, the patient noted bleeding from the nose and gums, and a purpuric rash on the legs. Physical examination revealed low grade fever, bilateral conjunctival hemorrhages, crusted blood in the nose, minimal bleeding from the gingivae, and a slightly enlarged spleen. The initial Rumpel-Leede's capillary

fragility test was markedly positive (4+). The bleeding time was over 20 minutes. The platelet count was 7,000 per c.mm. Sternal marrow aspiration revealed a normocellular marrow with adequate megakaryocytes which did not, however, appear to have been sequestering platelets.

Intramuscular cortisone was begun, 300 mg. on the first day, 200 mg. on the second, and thereafter 100 mg. a day, in divided doses. The formation of new petechiae and the bleeding from the mucous membranes ceased within 3 days after the beginning of cortisone therapy. On the seventh day of cortisone administration, the platelet count had risen to 150,000 per c.mm. and the Rumpel-Leede's test was negative (4 petechiae). Cortisone was administered until May 9 and the platelet count rose to values between 300,000 and 400,000 per c.mm.

After discharge from the hospital on May 16, 1951, the patient was followed in the outpatient department and did well for 6 months. Then, there was a progressive decline in platelets, and the menses became prolonged and profuse. The patient was, therefore, readmitted for cortisone therapy 9 months after the completion of the first course of treatment. The Rumpel-Leede's test was positive (3+) and the platelet count was 38,000 per c.mm. On February 28, cortisone was administered orally, 50 mg. every 6 hours for 4 doses, and then 50 mg. every 12 hours. On March 6, the platelet count had risen to 151,000. The Rumpel-Leede's test on March 18 was negative.

During the next 5 months the platelet count declined to levels ranging from 62,000 to 99,000 per c.mm. Because of extensive dental cavities and the necessity of tooth extractions, the patient was placed on oral cortisone treatment between October 22, 1952, and November 13, 1952. The platelet count rose to 666,000 while the patient was on therapy and the tooth extractions were accomplished without difficulty.

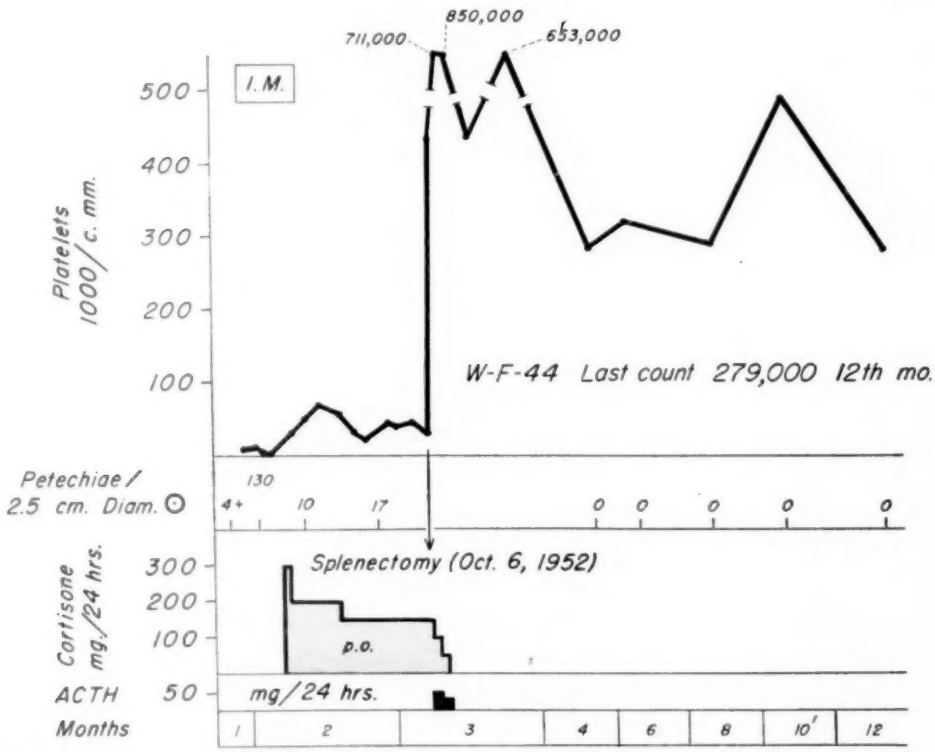

Fig. 2.—Patient I. M. Idiopathic thrombocytopenic purpura with improved capillary fragility but no significant platelet rise on cortisone therapy; apparent cure following splenectomy.

Since that time there has been a decline in the platelet level to as low as 54,000 per c.mm. There has been no excessive bleeding during the 14 months following the third course of cortisone therapy. The patient remains under observation.

Comment. This girl has had intermittent cortisone therapy on 3 occasions for thrombocytopenic purpura of unknown cause since April 25, 1951. The response to cortisone therapy on each occasion has been excellent but relapse has gradually followed cessation of therapy.

Leede's test (4+) and the bleeding time was 11½ minutes. The patient was placed on cortisone therapy with consequent improvement in capillary fragility so that the Rumpel-Leede's test became only slightly positive (1+). However, there was no sustained rise in platelet count. Laboratory studies also revealed positive serologic tests for syphilis.

Cortisone therapy was continued at the rate of 150 mg. per day for one month and when no sustained platelet rise occurred, splenectomy was performed on October 6, 1952 (preoperative platelet count numbered 28,000 per c.mm.). Cortisone was discontinued by the fourth postoperative day, and a small amount of ACTH was given. Splenec-

TABLE 1.—TESTS FOR SYPHILIS ON SERA FROM 2 PATIENTS WITH IDIOPATHIC THROMBOCYTOPENIC PURPURA

	Results			
	Case 2		*Case 4*	
Test[a]	*6/10/53*	*6/24/53*	*9/5/52*	*3/11/53*
Microflocculation				
Army cardiolipin	R	R	R	wr
Kline cardiolipin	R	R	R	wr
Rein-Bossak cardiolipin	R	R	R	wr
Mazzini	R	R	R	wr
Precipitation				
Kahn	wr	wr	R	—
Complement-fixation				
Army cardiolipin	R	R	R	—
Kolmer	R	R	—	—
Treponemal immobilization	—	—	—	—

R (reaction, 2 to 4 plus), wr (weak reaction, ± to 1 plus), — (no reaction)

[a] All tests performed by Dr. John F. Kent, Army Medical Service Graduate School, Washington, D. C.

CASE 2 (Fig. 2). I. M., a 44-year-old white female, was admitted September 1, 1952, with a history of easy bruisability for the past 10 to 12 years and slight bleeding from the gums on brushing the teeth. No other hemorrhagic manifestations had occurred.

The development of purpura in this patient was of especial interest to us since we were aware that the patient's daughter, aged 13 years, had died of cerebral hemorrhage due to idiopathic thrombocytopenic purpura one year before in another institution.

Physical examination revealed the blood pressure to be 180/100. The spleen was palpable 4 cm. below the left costal margin. There was a markedly positive Rumpel-

tomy was followed by a rapid increase of platelets to normal levels and the Rumpel-Leede's test was repeatedly negative. A complete clinical and hematologic remission persisted throughout 1953.

The results of 7 serologic tests for syphilis and of the treponema immobilization test on serum specimens collected September 5, 1952, and March 11, 1953, are shown in Table 1.

Comment. Capillary fragility was markedly improved by cortisone therapy without adequate platelet rise. Splenectomy, however, resulted in apparent cure. The treponema immobil-

ization test on this subject's sera was negative, in contrast to the positive findings with the serologic tests for syphilis.

CASE 3 (Fig. 3). M. F., a 78-year-old white female, first noticed the onset of purpura one month prior to her admission to Temple University Hospital on August 8, 1952. Except for the presence of ecchymotic and petechial hemorrhages in the skin, the physical examination was not remarkable. The Rumpel-Leede's test was strongly positive (3+), and the Duke bleeding time was 14½ minutes. The platelet count was only 20,000 per c.mm., but the bone-marrow aspirate appeared to contain an adequate number of megakaryocytes.

The patient was placed on oral cortisone therapy on August 14, 1952, and the dosage was maintained at 150 mg. per day until October 8, 1952. At no time was there an adequate platelet response although capillary fragility was greatly reduced. Splenectomy was performed on October 8, after almost 2 months of continuous cortisone treatment. A small amount of ACTH was administered during the immediate postoperative period, and at the same time, the cortisone dosage was progressively reduced. On October 21, the Rumpel-Leede's test was negative. While this patient's platelets did not rise to normal levels for any sustained period of time following splenectomy, there was achieved a clinical remission.

Comment. This unusual instance of idiopathic thrombocytopenic purpura in a 78-year-old woman again demonstrated the dichotomy of response of capillary endothelium and platelets to cortisone therapy. Splenectomy was followed by a suboptimal hematologic result.

CASE 4 (Fig. 4). Sa. M., a 60-year-old white female was first admitted to Temple University Hospital in 1949, for chronic calculous cholecystitis. A platelet count done at that time preoperatively, when no hematologic disorder was apparent, revealed 129,000 per c.mm. The second admission occurred on July 29, 1952, at which time the patient gave a history of spontaneous bruising for 5 months, and she had noticed nosebleeds for 10 months. Examination revealed numerous ecchymoses over the extremities. The Rumpel-Leede's test was strongly positive (4+) and the average of several platelet counts was 35,000 per c.mm. The serologic test for syphilis was positive, as were the direct and indirect Coombs' tests. On August 2, Compound F was begun, 225 mg. the first day, then 150 mg. daily in 3 divided doses by intramuscular injection. Treatment was continued at

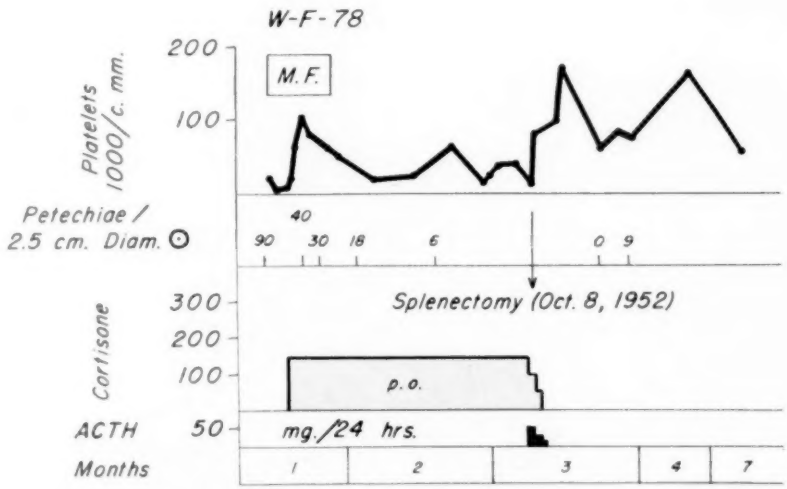

Fig. 3.—Patient M. F. Idiopathic thrombocytopenic purpura with suboptimal platelet response following splenectomy after failure to achieve remission with cortisone.

this dosage level until August 23, without significant response either in platelet count or in capillary fragility. On August 26, intramuscular cortisone therapy was begun, 225 mg. the first day and then 150 mg. in divided doses. By August 29, the platelet count was 236,000 and the spontaneous ecchymoses had ceased. The patient's platelet count was maintained at approximately this level until intramuscular cortisone was stopped on September 6, when the patient was discharged from the hospital. Following discharge, cortisone was administered orally, 150 mg. daily until September 18, at which time the platelet count was 162,000 and the drug was discontinued. A subsequent fall in the platelet count occurred so that on November 25, the platelet count was 31,000 per c.mm. and the Rumpel-Leedes' test was 4+ positive. Compound F by mouth was then begun at the dosage level of 60 mg., 3 times a day. The platelet count rose to 252,000 per c.mm. on December 1, and the Rumpel-Leede's test revealed no petechiae. The dose of Compound F was then reduced to 40 mg., 3 times a day by mouth. On this dosage the patient maintained a platelet level of about 150,000 per c.mm. and a negative Rumpel-Leede's test until December 16, at which time Compound F was discontinued. By January 12, the platelet count had again fallen to 16,000 per c.mm. and the Rumpel-Leede's test elicited numerous petechiae (4+). Compound F was again administered orally, 40 mg., t.i.d., and by January 19, the platelet count had risen to 115,000 with 5 petechiae elicited by the Rumpel-Leede's test. The patient was, therefore, readmitted to the hospital on January 26, and splenectomy was performed January 28, while the patient was being maintained on oral Compound F therapy. On the day of operation, the Rumpel-Leede's test was negative and the platelets numbered 96,000 per c.mm. On January 29, 1953, the first postoperative day, the platelet count rose to 844,000 per c.mm. On March 10, the platelet count was 555,000 per c.mm. High platelet counts and complete clinical remission have persisted to the time of this writing.

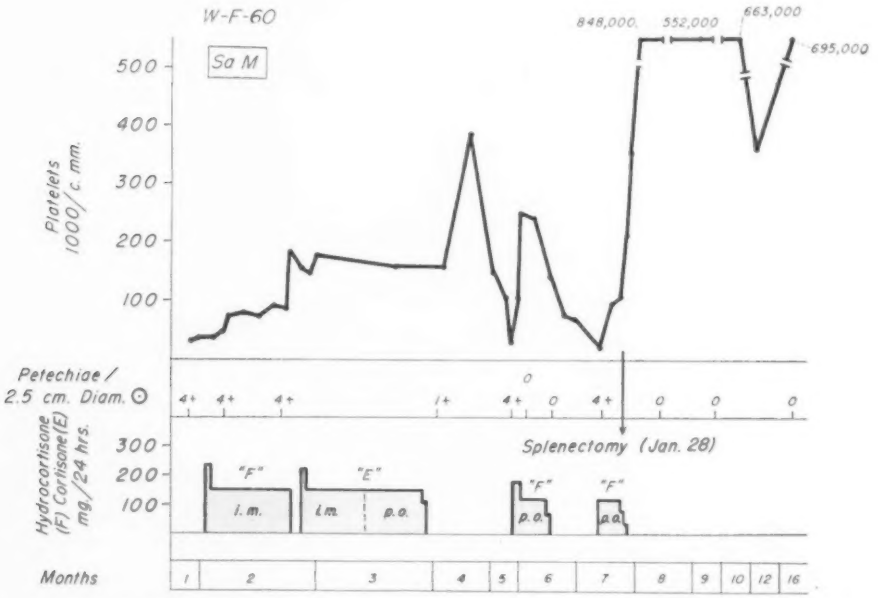

Fig. 4.—Patient Sa. M. Intramuscular Compound F failed to improve capillary fragility or platelet level, while temporary remissions resulted with intramuscular cortisone, oral cortisone, and oral Compound F. Splenectomy resulted in sustained clinical and hematologic remission.

Comment. This patient illustrates the fact that Compound F when injected intramuscularly is not disseminated

throughout the body and, therefore, its use did not induce a response in the platelet count or improve capillary permeability. However, oral cortisone and oral Compound F appeared equally effective in producing a platelet rise and in reducing capillary fragility in this patient. Permanent remission, however, could not be obtained with steroid therapy and the patient had to be maintained almost continuously on either Compound E or F until splenectomy was performed. Following splenectomy, however, there has been a sustained clinical and hematologic remission.

It is also of interest that this patient had positive serologic tests for syphilis, but negative treponema immobilization tests. (Table 1).

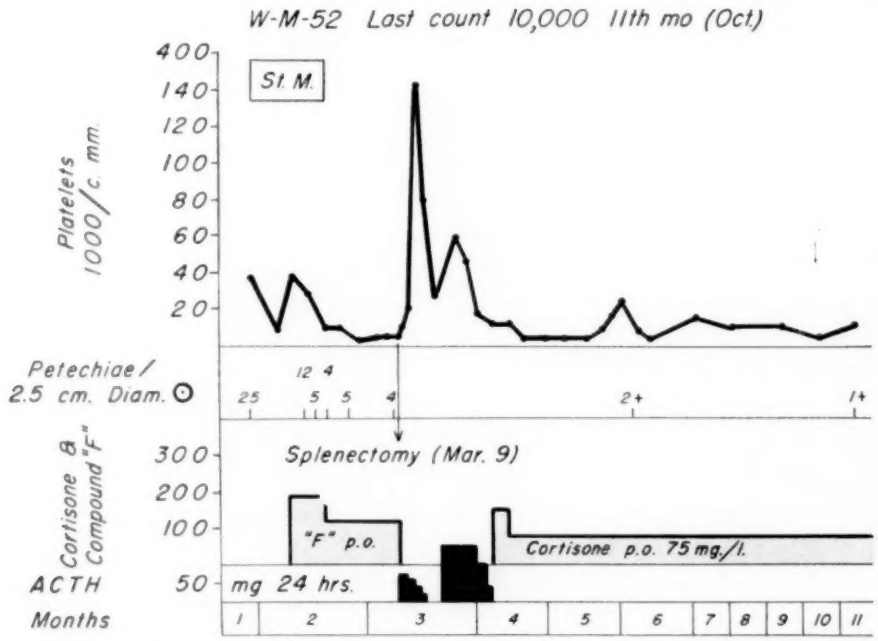

Fig. 5.—Patient St. M. Administration of Compounds E, F, and ACTH, and splenectomy have failed to produce satisfactory platelet remission. Capillary fragility is reduced on maintenance cortisone therapy.

CASE 5 (Fig. 5). St M. is a 52-year-old white male whose past medical history is of interest in that he has had episodic nosebleeds since childhood. He recalls being treated by physicians or in hospitals in 1909, 1910, 1918, 1919, 1935, and on several other occasions since that time because of epistaxis. In 1935, the patient was referred to another hospital because of a finding of sugar in the urine. During that admission, a low platelet count was discovered and splenectomy was advised but was not performed. At that time the patient also had a doubtful serology and was eventually treated with bismuth and iodides and with fever therapy because of a diagnosis of central nervous system syphilis. On January 13, 1953, the patient fell off a ladder and badly bruised his left side. The patient was admitted to another hospital where a platelet count was reported as 170,000 per c.mm. A short convulsive seizure occurred during this hospitalization but skull films and spinal fluid examinations were negative. The patient was discharged on January 20, 1953. Between January 22, and the date of his admission, January 28, to Temple University Hospital, the patient had at least 4 episodes of severe epistaxis one of which

required brief hospitalization elsewhere for transfusion therapy.

At Temple University Hospital the significant findings were scattered generalized ecchymoses and almost complete bruising of his left side. There was pallor of the mucous membranes. The Rumpel-Leede's test on admission was positive (2+) and the platelets numbered 37,000 per c.mm. Bone-marrow examination revealed a normocellular marrow with numerous megakaryocytes which showed little evidence of sequestration of platelets. On February 9, the patient was begun on 60 mg. of Compound F, 3 times a day by mouth. Capillary fragility improved rapidly as judged by repeated Rumpel-Leede's tests. On February 19, the Compound F dosage was decreased to 40 mg. orally 3 times a day. Repeated counts showed no increase of platelets, however, and splenectomy was therefore performed on March 9. ACTH, 25 mg. intramuscularly every 8 hours was given for 3 doses prior to splenectomy along with the oral Compound F. The Compound F was discontinued postoperatively, but ACTH was continued until March 11, when tapering off of the doses was begun. Postoperatively there was a transitory increase in platelets to 143,000 per c.mm. The question arose as to whether this was consequent to the ACTH therapy or to the splenectomy. Since on March 21, the platelets numbered only 32,000 per c.mm., ACTH, 50 mg. every 8 hours, intramuscularly, was begun and continued until April 1. During this period, there was no platelet response suggesting that the transient rise in platelets previously noted had been consequent to splenectomy. On April 2, oral cortisone therapy was resumed, 50 mg. every 8 hours. This was reduced, on April 6, to 25 mg. every 8 hours, at which level it has been maintained to the present.

The patient had an extremely difficult postoperative course. On April 3, the patient suffered a right hemiparesis from which he completely recovered in 24 hours. There were several episodes of temperature elevations to 102° for which no cause could be found. At one time he had marked hyperparesthesia of his left side with referred pain to the left shoulder and left jaw. A tachycardia and gallop rhythm developed and electrocardiographic signs of posterior myocardial infarction appeared. Signs of a subphrenic collection also appeared on the left side and on April 18, 800 cc. of old hemolyzed blood were obtained from the left subphrenic space by needle aspiration. The febrile elevations did not respond to aureomycin nor to high dosage salicylates. On May 9, 1953, methyl testosterone, 5 mg. orally, was added to his program. He was discharged from the hospital on June 10, 1953, to continue taking 75 mg. of cortisone and 5 mg. of methyl testosterone daily. In addition, sodium intake was restricted while potassium supplements were continued. On this program, the patient gradually gained in strength and weight, and he was able to return to work as an electrician in September, 1953. Platelet counts have ranged from 4,000 to 37,000 per c.mm., and the Rumpel-Leede's test remains moderately positive. Despite these findings, however, there have been no bleeding phenomena.

Comment. This patient's history indicates a chronic, recurrent thrombocytopenic purpura of many years' duration. Compounds F and E, ACTH and splenectomy have all failed to induce a satisfactory platelet remission. Cortisone therapy is being continued indefinitely, however, for its favorable effect on capillary fragility.

CASE 6 (Fig. 6). J. L. T., a 39-year-old colored female, was admitted to Temple University Hospital on Gynecology Service, December 4, 1952, because of a 3 months' history of severe menometrorrhagia. Admission blood studies revealed a hemoglobin of 6.4 gm. per 100 cc., and the bleeding time was 5 minutes. Transfusions were administered and dilatation and curettage was performed on December 8. Because of persistent vaginal hemorrhage and the presence of fibromyoma uteri, hysterectomy was attempted on December 11, but the surgeon noticed severe wound bleeding. Since 700 cc. of blood had been lost, the wound was closed without proceeding through the peritoneum. Emergency hematologic consultation was requested and immediate blood studies were undertaken. These revealed a 49,000 platelet count, the Lee-White coagulation time was 12¾ minutes and there was poor clot retraction. The prothrombin time performed the day after operation gave a value of 44%. The bleeding time on this date was 12 minutes. Platelet counts were done over the next week and yielded values varying from 75,000 to 115,000 per c.mm. Prolongation of the coagulation time (20.5 minutes and 29.5 minutes) and poor clot retraction were observed. Other tests performed and found to be negative were tests for sickle cells, liver function studies, the direct Coombs' test, tests for circulating anticoagulants, for fibrinolysis and for afibrinogenemia. In spite of the generally

low platelet count and the persistence of hemorrhagic oozing from the wound and vaginal bleeding, the Rumpel-Leede's test remained consistently negative. Although large daily doses of parenteral vitamin K were administered, severe vaginal bleeding occurred on December 28, so that the patient's hemoglobin fell to 5.3 gm. per 100 cc. The patient was transfused with 1000 cc. of blood and Compound E was begun at a dosage level of 225 mg. per day for 3 days, followed by a maintenance dose of 150 mg. per day. The control studies the day before beginning discharged and cortisone was continued, 100 mg. daily in 4 divided doses, until January 26, when it was tapered off and stopped. Platelets numbered 154,000 per c.mm. and the patient was asymptomatic.

She remained well and had normal menses until menorrhagia occurred in June and again in July. Blood loss was great and she was readmitted to the hospital on July 29, 1953. At this time the hemoglobin was 4.3 gm. per 100 cc., and the platelet count was 47,000 per c.mm. Cortisone was administered as before, and again there was a rapid rise

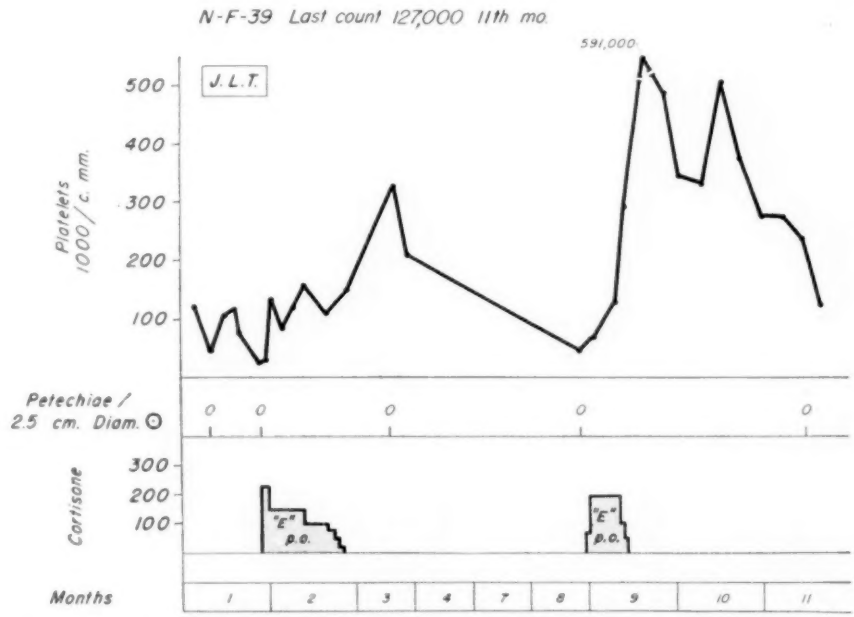

Fig. 6.—Patient J. L. T. Platelet remission induced after 2 courses of cortisone therapy, and after one of Compound F. (not shown in chart). Note negative Rumpel-Leede's test throughout.

Compound E revealed 26,000 platelets per c.mm., bleeding time of 15½ minutes, and a Lee-White coagulation time of 13 minutes. The Rumpel-Leede's test remained negative. The administration of Compound E was followed by an immediate decrease in the severity of wound bleeding and vaginal bleeding ceased entirely. The platelet count at this point was only 83,000 per c.mm. By January 12, the platelets had risen to 157,000 per c.mm. and the bleeding and coagulation times were normal and clot retraction was good. The patient refused permission for hysterectomy at this time. She was, therefore, in platelets and cessation of vaginal bleeding. Cortisone was continued until August 22, at which time the platelets numbered 591,000 per c.mm.

During the succeeding months the platelet counts were done weekly and while the values fluctuated considerably, there was a general downward trend. Menorrhagia appeared in late December 1953, and the platelet count was 35,000 per c.mm. on December 26. Treatment was resumed, this time with Compound F, 40 mg. orally every 8 hours. There was again noted prompt cessation of vaginal bleeding and the platelets increased

to 133,000 per c.mm. on the twelfth day of therapy. Treatment is in progress at the present time.

Comment. This patient has had 3 episodes of severe vaginal bleeding, but no concomitant purpura despite low platelet values. Furthermore, the Rumpel-Leede's test has been consistently negative. While transitory clinical and hematologic improvement followed 2 courses of cortisone therapy and one of Compound F, splenectomy is contemplated.

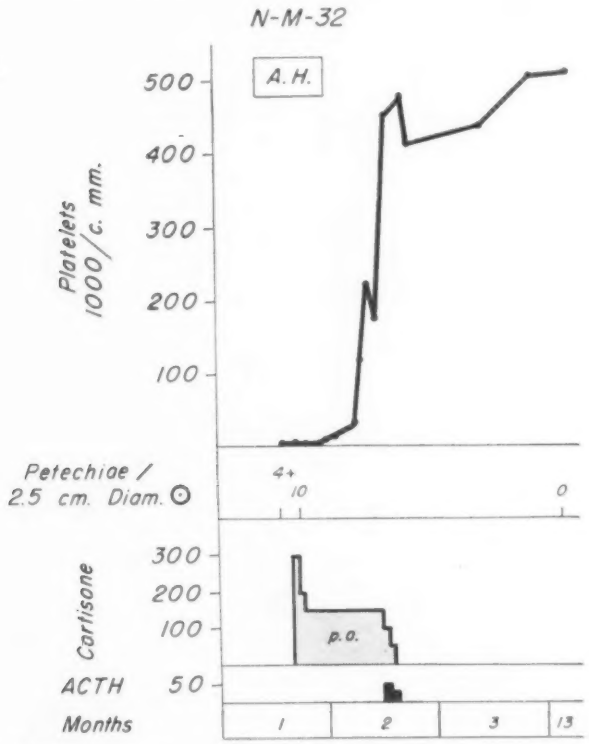

Fig. 7.—Patient A. H. Sustained clinical and hematologic remission after one course of oral cortisone therapy.

CASE 7 (Fig. 7). A. H., a 32-year-old Negro male, was in good health until March 15, 1952, at which time he developed bleeding of gums and noticed that his stools were darker than usual. The gingivae continued to bleed and mild epistaxis occurred on March 17, at which time he was admitted to Temple University Hospital.

Physical examination on admission revealed a well-developed adult Negro male in no acute distress. Examination was negative except for the following: (1) several large maculopapular purpuric areas on the tongue, buccal mucosa and lips; (2) gingivae oozing blood; (3) scattered petechiae on the abdomen and extremities. The liver and spleen were not palpable. The Rumpel-Leede's test was markedly positive.

Laboratory examination on admission revealed no platelets. The bone-marrow aspirate was actively cellular with adequate megakaryocytes which did not appear to be sequestering platelets.

During his early course in the hospital the gums continued to bleed, the patient was febrile (99 to 102°) and both upper and lower gastrointestinal bleeding occurred.

On March 21, 1952, the patient was started on a course of cortisone (300 mg. first 24 hours, 200 mg. second 24 hours, and 150 mg. every 24 hours thereafter in divided doses). The Rumpel-Leede's test was negative by March 23 and there was prompt cessation of the hemorrhagic phenomena. Repeat sternal marrow examination on April 16, again showed numerous megakaryocytes which, at this time, were sequestering platelets.

Beginning on April 15, the cortisone dosage was gradually diminished and ACTH was given for the purpose of adrenal stimulation. All therapy ceased on April 22, and the patient was discharged on April 23, 1952.

One year later, on March 17, 1953, the patient was asymptomatic with a platelet count of 508,000 per c.mm.

Comment. After institution of cortisone therapy this patient had an excellent clinical and hematologic remission which has been sustained for more than one year.

CASE 8 (Fig. 8). D. S., a 38-year-old white female, was admitted to Temple University Hospital on February 5, 1953, because of convulsive episodes. On February 13, a left meningioma was removed uneventfully and the patient was discharged on February 25. Several days after discharge the patient developed generalized purpura with a positive Rumpel-Leede's test. The platelet count was 32,000 per c.mm.

The patient returned as an outpatient, and oral Compound F was begun at a dosage level of 40 mg. every 8 hours on March 16, when control studies revealed 93,000 platelets per c.mm. and a 4+ capillary fragility test. By March 20, the fourth day after beginning Compound F, the Rumpel-Leede's test was negative and by March 27, the platelet count had risen to 390,000 per c.mm. Compound F was reduced to 20 mg. every 8 hours until it was discontinued on April 8, 1953.

The patient has remained asymptomatic to date.

Comment. It is possible that this patient would have experienced a spontaneous remission in due time. In view of the recent cerebral surgery, however,

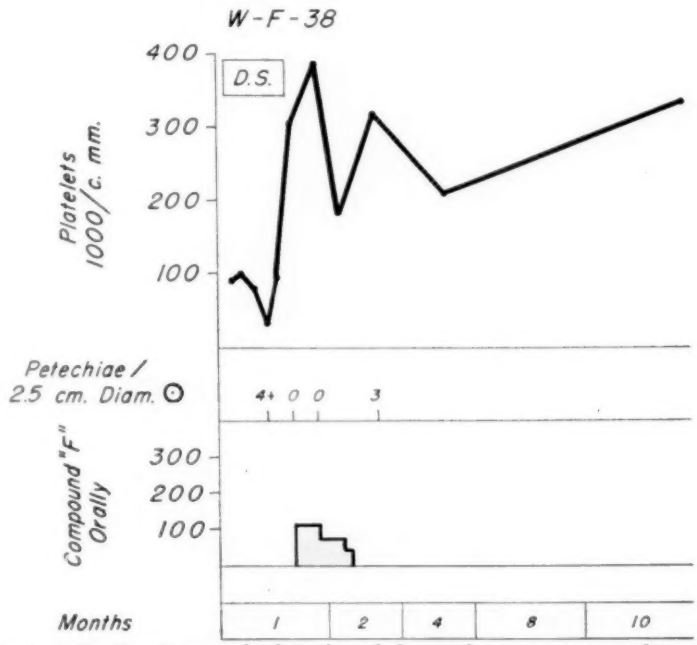

Fig. 8.—Patient D. S. Sustained clinical and hematologic remission after single course of oral hydrocortisone therapy.

it was considered especially hazardous to follow a course of watchful waiting in this case.

CASE 9 (Fig. 9). M. A., a 14-year-old white schoolgirl, was admitted to Temple University Hospital March 12, 1953, because of acute severe epistaxis. Admission studies revealed a markedly positive Rumpel-Leede's test, 17,000 platelets per c.mm., and bleeding time, 25 minutes. The bone-marrow aspirate contained numerous megakaryocytes.

On March 14, oral Compound F therapy was begun. On 60 mg. every 8 hours, the nasal bleeding ceased promptly and the Rumpel-Leede's test was negative by March 16. However, the platelet rise was suboptimal after 2 weeks, and ACTH, 50 mg. every 8 hours intramuscularly was substituted for Compound F. The platelet response was still suboptimal when ACTH was discontinued at the time of discharge on April 12, 1953. The patient was asymptomatic and platelets numbered 125,000 per c.mm.

One month after discharge the platelet count was 44,000 per c.mm. and the Rumpel-Leede's test was again strongly positive. Compound F administration was resumed on May 11, 20 mg. orally, every 6 hours. After one week of therapy the platelet count was 114,000 per c.mm., and the Rumpel-Leede's test was only slightly positive. Compound F was discontinued on June 3 at which time the patient was in clinical remission. She has remained well although the platelet counts have ranged less than 125,000 per c.mm.

Comment. Both oral Compound F and intramuscular ACTH were effective in reducing capillary fragility and in increasing platelet counts. The platelet rise was suboptimal on each occasion, however, and was not maintained when therapy was stopped. The patient remains under observation, and splenectomy is contemplated in the event of recurrence of hemorrhagic phenomena.

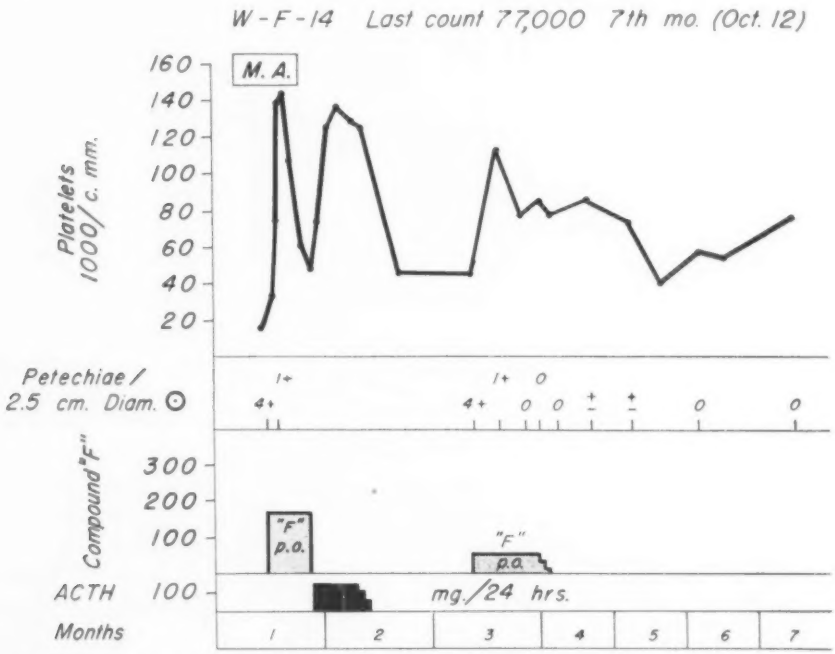

Fig. 9.—Patient M. A.—Temporary clinical and hematologic remissions after treatment with oral Compound F (2 courses) and intramuscular ACTH.

CASE 10. B. A. S., a 16-year-old schoolgirl, was admitted to Temple University Hospital

on November 30, 1953, because of recurrent epistaxis. She had been well until, at the age of 10 years, spontaneous bleeding from the nose was experienced one or 2 times a month. Over the succeeding 6 years these episodes became progressively more frequent. In addition, she was aware of easy bruisability, and gingival bleeding on brushing of her teeth. The menses, however, had not been associated with excessive blood loss.

Examination revealed ecchymoses on the left arm and both thighs, but was otherwise not remarkable. The Rumpel-Leede's test was strongly positive. The bleeding-time (Duke) was prolonged to more than 20 minutes, and the platelets numbered 30,000 per c.mm. The bone-marrow aspirate was of good cellularity and numerous megakaryocytes were present.

Extensive allergic studies were noncontributory.

Compound F, 40 mg. every 8 hours, was administered orally from December 12 through December 30. The dosage was then gradually reduced and the drug discontinued on January 2, 1954. The Rumpel-Leede's test became negative by the third day of therapy, and the platelet count rose progressively to 464,000 per c.mm. by January 4, 1954.

Comment. Although oral Compound F therapy apparently induced an excellent remission in this case, further observation will be necessary before the result can be finally assessed.

CASE 11. M. T. G., a 24-year-old colored housewife, was admitted to Temple University Hospital on January 20, 1954, because of epistaxis of 2 days' duration. A hematoma appeared spontaneously on the dorsum of the right hand the day prior to admission. There was no history of other abnormal bleeding phenomena, or of allergy.

Upon admission, the blood pressure was 130/98; numerous petechiae appeared below the level of application of the sphygmomanometer cuff. Ecchymotic areas were present on both thighs, and on the dorsal surface of the right hand. Hemorrhagic crusts were noted in the nares. The liver and spleen were not palpable.

The bleeding time exceeded 30 minutes, and platelet counts ranged from 23,000 to 30,000 per c.mm. Numerous megakaryocytes were present in the bone-marrow aspirate.

Compound F therapy was instituted on January 26, 40 mg., orally, every 8 hours. This schedule was maintained until February 16 and then, after a brief tapering-off period, the Compound F was discontinued. There have been no hemorrhagic manifestations and platelet counts exceeded 500,000 per c.mm. during the 6 weeks' follow-up period to date.

Comment. Compound F therapy was associated with an excellent clinical and hematologic result in this case.

Extended follow-up observation is, of course, planned for this patient as well as for all of the preceding subjects.

Results. EFFECT OF THERAPY ON PLATELETS. A rise in the number of platelets was not uniformly elicited. Three of the patients had little or no platelet response to therapy with cortisone (2 cases) and Compound F (one case), and were subjected to splenectomy. One appears to have been cured by the operation, a second experienced a suboptimal platelet remission, while the third had an ephemeral rise in platelets and has since had marked thrombocytopenia (10 months postoperative). A fourth patient who had satisfactory but temporary platelet remissions on cortisone and on Compound F also appears to have been cured by splenectomy.

Of the remaining 7 patients, adequate platelet remissions have resulted during each course of cortisone or Compound F therapy. Two individuals appear to be cured of their disease, while 2 other cases are pending. All 4 of these subjects received only a single course of oral Compound F. Three other patients have had a total of 8 courses of steroid therapy. Platelet remissions have been induced on each occasion, but gradual relapse occurred following cessation of therapy. These patients remain under observation and may ultimately be subjected to splenectomy.

EFFECT OF THERAPY ON CLINICAL BLEEDING AND CAPILLARY RESISTANCE. In all cases where clinical bleeding was present, it was promptly controlled by

steroid therapy. Improvement in capillary resistance, as measured by the Rumpel-Leede's test, was also uniformly observed. These effects were noted during therapy with cortisone (8 courses, orally; 2, intramuscularly), Compound F (8 courses, orally), and ACTH (2 courses, intramuscularly). Parenteral Compound F was ineffective in one patient (Case 4), but its oral administration to the same subject induced a remission on 2 occasions. The improvement in capillary resistance was sustained as long as therapy was continued even in the absence of a platelet remission.

With regard to the other tests performed during the course of this study, it should be noted that "L.E." cell preparations were negative throughout. Positive Coombs' tests were obtained in 3 cases, and 2 patients had repeatedly positive serologic tests for syphilis. However, sera from these 2 patients gave negative results in the treponemal immobilization test.

Discussion. Although the etiology of idiopathic thrombocytopenic purpura remains obscure, considerable evidence has accumulated which implicates a disturbance in auto-immune mechanisms as an important factor at least in some cases. In this connection, it should be noted that positive Coombs' tests were obtained in 3 of these 11 patients. Two of the subjects also had repeatedly positive serologic tests for syphilis. Representative serum specimens, however, yielded negative results in the treponemal immobilization test, indicating that the serologic tests were falsely positive. These cases illustrate the usefulness and value of the treponemal immobilization test as an aid in the differentiation of false-positive serology from reactions due to luetic infection. Such differentiation has greater significance than simply serving to prevent an erroneous diagnosis and an unnecessary course of antiluetic therapy. False-positive tests for syphilis, even when recognized as such, can no longer be viewed as mere annoyances. Rather, persistently positive serology of nonluetic origin may instead indicate an auto-immune disturbance which may later become manifest as idiopathic thrombocytopenic purpura, acquired hemolytic anemia, or disseminated lupus erythematosus. Therefore, patients who have false-positive serologic tests for syphillis, for which there is no ready explanation, should undergo careful follow-up studies.

It is evident from the results in these 11 cases of idiopathic thrombocytopenic purpura, that the response of the platelets to cortisone or to oral Compound F therapy was variable. Moreover, even when a remission did follow such therapy, there appeared to be no way of predicting whether or not the effect would be sustained after treatment was discontinued. This observation is consistent with the experience of others[7,8,10,11] with regard to cortisone. From the findings described herein, there appears to be no qualitative difference between the results achieved with Compound F as compared with cortisone. It was of interest, however, to note that parenteral Compound F was ineffective in one patient, while the same amount of Compound F, orally, and of cortisone administered either parenterally or orally, was in each instance followed by clinical and hematologic remission.

In contrast to the variability of the platelet response, however, improvement in capillary resistance was uniformly observed following steroid therapy. Thus, these agents are ideally suited to the emergency treatment of idiopathic thrombocytopenic purpura. Furthermore, if splenectomy is deemed necessary, preoperative preparation with steroid therapy minimizes the

risks attending surgery. It is our practice to continue such therapy during and for several days after operation. No difficulty with wound healing has been encountered in patients so treated.

It is our belief that properly controlled therapy with cortisone, hydrocortisone, or ACTH, initiated at the time of diagnosis, constitutes a conservative approach to the management of idiopathic thrombocytopenic purpura. To be sure, a significant percentage of cases undergoes spontaneous remission. However, a patient may bleed into a vital area while one stands by hoping that the natural course of the disease will progress to spontaneous remission. Thus, an attitude of watchful waiting is fraught with danger and, in our opinion, can no longer be justified.

Summary and Conclusions. 1. Eleven patients with idiopathic thrombocytopenic purpura were treated with cortisone, hydrocortisone, and ACTH.

2. Clinical bleeding was halted and capillary resistance uniformly improved on steroid therapy; platelet remissions, temporary or permanent, were observed in 8 of the 11 cases.

3. There appeared to be no qualitative difference between the results achieved with oral hydrocortisone and those obtained with cortisone.

4. Persistently positive serologic tests for syphilis were obtained in 2 cases. These were shown to be false-positive through use of the treponema immobilization test.

5. It is concluded that steroid therapy initiated at the time of diagnosis of idiopathic thrombocytopenic purpura is more conservative than a program of watchful waiting.

ACKNOWLEDGMENTS: The authors wish to thank Dr. John F. Kent for performing treponemal immobilization and special serologic tests for syphilis on sera from 2 of these patients. Grateful appreciation is also expressed to Miss Virginia F. Colville for technical assistance in the course of this study.

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THE SYNERGISTIC AMEBICIDAL EFFECT OF TETRACYCLINE, OXYTETRACYCLINE AND CARBOMYCIN ON CULTURES OF ENDAMEBA HISTOLYTICA*

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The most recent discovery in the antibiotic field is tetracycline which is very similar to oxytetracycline (Terramycin) and chlortetracycline (Aureomycin). Its antibacterial spectrum, pharmacology, as well as therapeutic properties are similar to oxytetracycline and chlortetracycline. It inhibited 22 different species of Gram-positive bacteria in a concentration of 0.312 to 1.56 mcg./cc., but *Corynebacterium diphtheriae* and *C. xerosis* were inhibited in a concentration of 6.25 mcg./cc. Fifteen different species of Gram-negative bacteria were inhibited in 0.39 to 3.12 mcg./cc., but *Pseudomonas aeruginosa* was inhibited in 25 mcg./cc., and *Proteus vulgaris* was not inhibited in a concentration of 100 mcg./cc. Tetracycline showed no activity against a *Micrococcus pyogenes* var. *aureus* strain which was resistant to oxytetracycline and chlortetracycline, or to these two plus several or all of the other antibiotics (penicillin, chloromycetin, polymyxin, bacitracin), showing a nearly complete cross resistance between tetracycline, oxytetracycline and chlortetracycline. Tetracycline (Tetracyn) does not cross resist with either carbomycin (Magnamycin) or with a combination of penicillin plus streptomycin[1,2,6].

Magnamycin (carbomycin) was reported to have amebicidal properties[8]. Subsequent clinical studies indicated that Magnamycin was very effective in the treatment of clinical amebiasis[7,9]. The amebicidal properties of Terramycin (oxytetracycline) have already been established, so that it is the drug of choice in amebiasis[3-5].

The present studies were undertaken to compare the *in vitro* amebicidal effect of oxytetracycline and tetracycline on cultures of *Endameba histolytica*, and the synergistic amebicidal effect on *E. histolytica* cultures of oxytetracycline or tetracycline plus carbomycin, and oxytetracycline plus tetracycline.

Method. PREPARATION OF THE MEDIUM. The contents of 8 fresh eggs were emulsified in 100 cc. buffered saline† in a sterile flask containing beads. Three to 4-cc. amounts were put in sterile test tubes and inspissated in slanting position at 90° C., 15 pounds pres-

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†M/15 $Na_2HPO_4.7H_2O$, M.W. 268.09 (1.72 gm. per 100 cc.) 82.0 cc.
M/15 KH_2PO_4 (0.907 gm. per 100 cc.) 5.0 cc.
NaCl C.P. 8.5 gm.
Distilled water q.s. 1000.0 cc.
Sterilize at 15 pounds pressure for 5 minutes

sure for 90 minutes. Immediately before use, 5 cc. buffered saline and sterile rice starch (sterilized at 145° C. in dry heat for 90 minutes) were added.

Columbia, Gloria and Korea strains of *E. histolytica*, *E. histolytica* with *Escherichia coli*, *E. histolytica* with *Aerobacter aerogenes* and *E. histolytica* with *Clostridium perfringens* were grown for 48 hours on this medium in which the overlay was buffered saline.

Carbomycin, oxytetracycline and tetracycline, and equal quantities (by weight) of carbomycin plus oxytetracycline, carbomycin plus tetracycline, and tetracycline plus oxytetracycline were serially diluted in buffered saline in the following concentrations: 1,000, 500, 250, 125, 62.5, 31.25, 15.625 and 7.81 mcg./cc. Five cubic centimeter amounts of the diluted antibiotic or antibiotic combinations were put in the medium, to which was then added sterile rice starch. The tubes were then inoculated with approximately 50,000 actively growing 48-hour old *E. histolytica* trophozoites of the above mentioned six strains of ameba. The tubes were incubated for 48 hours and the contents were examined at 24- and 48-hour intervals under the low and high power of the microscope for the presence or absence of ameba.

Results. Table 1 shows the effect of oxytetracycline, carbomycin, and equal concentrations of oxytetracycline plus carbomycin on 5 strains of *E. histolytica* cultures. Oxytetracycline inhibited Korea in 250 mcg./cc.; Columbia, Gloria and *E. histolytica* with *A. aerogenes* in 125 mcg./cc.; and *E. histolytica* with *E. coli* in 31.25 mcg./cc. Carbomycin inhibited Columbia, Gloria and Korea strains in 1,000 mcg./cc.; *E. histolytica* with *A. aerogenes* in 500 mcg./cc.; and *E. histolytica* with *E. coli* in 125 mcg./cc. Equal amounts of oxytetracycline and carbomycin inhibited Columbia, Gloria and Korea strains in 62.5 mcg./cc.; *E. histolytica* with *E. coli* and *E. histolytica* with *A. aerogenes* in 15.625 mcg/cc.

Table 2 shows the effect of tetracycline, carbomycin and equal concentrations of tetracycline and carbomycin on cultures of *E. histolytica*. Tetracycline

TABLE 1.—THE EFFECT OF OXYTETRACYCLINE, CARBOMYCIN AND EQUAL CONCENTRATIONS OF OXYTETRACYCLINE PLUS CARBOMYCIN ON CULTURES OF ENDAMEBA HISTOLYTICA

Strains of E. histolytica	*Mcg./cc.*								
	1,000	*500*	*250*	*125*	*62.5*	*31.25*	*15.625*	*7.81*	*Control*
					Oxytetracycline				
Columbia	−	−	−	−	+	+	+	+	+
Gloria	−	−	−	−	+	+	+	+	+
Korea	−	−	−	+	+	+	+	+	+
E. histolytica with *E. coli*	−	−	−	−	−	−	+	+	+
E. histolytica with *A. aerogenes*	−	−	−	−	+	+	+	+	+
					Carbomycin				
Columbia	−	+	+	+	+	+	+	+	+
Gloria	−	+	+	+	+	+	+	+	+
Korea	−	+	+	+	+	+	+	+	+
E. histolytica with *E. coli*	−	−	−	−	+	+	+	+	+
E. histolytica with *A. aerogenes*	−	−	+	+	+	+	+	+	+
					Oxytetracycline plus Carbomycin				
Columbia	−	−	−	−	−	+	+	+	+
Gloria	−	−	−	−	−	+	+	+	+
Korea	−	−	−	−	−	+	+	+	+
E. histolytica with *E. coli*	−	−	−	−	−	−	−	+	+
E. histolytica with *A. aerogenes*	−	−	−	−	−	−	−	+	+

inhibited Korea strain in 250 mcg./cc.; and Columbia and *E. histolytica* with *A. aerogenes* in 125 mcg./cc.; while Gloria strain was inhibited in 62.5 mcg./cc. Carbomycin inhibited Korea, Columbia and *E. histolytica* with *A. aerogenes* in 1,000 mcg./cc. and Gloria in 500 mcg./cc. Equal concentrations of tetracycline and carbomycin inhibited Korea in 125 mcg./cc.; Gloria and Columbia in 62.5 mcg./cc. while *E. histolytica* with *A. aerogenes* was inhibited in 15.625 mcg./cc.

tica with *E. coli* and *E. histolytica* with *Cl. perfringens* in 15.625 mcg./cc.

Discussion. A comparison of the inhibitory effects of oxytetracycline and tetracycline on 6 strains of *E. histolytica* cultures revealed that oxytetracycline inhibited one strain of *E. histolytica* in a concentration of 125 to 250 mcg./cc.; three strains in 125 mcg./cc., one strain in 62.5 to 125 mcg./cc. and one strain in 31.25 mcg./cc.; whereas tetracycline inhibited one strain in a concentration of 125 to

TABLE 2.—THE EFFECT OF TETRACYCLINE, CARBOMYCIN AND EQUAL CONCENTRATIONS OF TETRACYCLINE AND CARBOMYCIN ON CULTURES OF ENDAMEBA HISTOLYTICA

Strains of E. histolytica	*Mcg./cc.*								
	1,000	*500*	*250*	*125*	*62.5*	*31.25*	*15.625*	*7.81*	*Control*
					Tetracycline				
Columbia	−	−	−	−	+	+	+	+	+
Gloria	−	−	−	−	−	+	+	+	+
Korea	−	−	−	+	+	+	+	+	+
E. histolytica with *A. aerogenes*	−	−	−	−	+	+	+	+	+
					Carbomycin				
Columbia	−	+	+	+	+	+	+	+	+
Gloria	−	−	+	+	+	+	+	+	+
Korea	−	+	+	+	+	+	+	+	+
E. histolytica with *A. aerogenes*	−	+	+	+	+	+	+	+	+
					Tetracycline plus Carbomycin				
Columbia	−	−	−	−	−	+	+	+	+
Gloria	−	−	−	−	−	+	+	+	+
Korea	−	−	−	−	+	+	+	+	+
E. histolytica with *A. aerogenes*	−	−	−	−	−	−	−	+	+

Table 3 shows the effect of oxytetracycline, tetracycline and equal concentrations of oxytetracycline plus tetracycline on 5 strains of *E. histolytica* cultures. Oxytetracycline and tetracycline inhibited Gloria, Korea and *E. histolytica* with *Cl. perfringens* in 125 mcg./cc., while *E. histolytica* with *E. coli* and Columbia strains were inhibited in 62.5 mcg./cc. Equal concentrations of oxytetracycline plus tetracycline inhibited Columbia and Korea strains in 31.25 mcg./cc.; and Gloria, *E. histolytica* with *A. aerogenes* in 250 mcg./cc., two strains in 125 mcg./cc. and one strain in 62.5 to 125 mcg./cc. and two strains in 62.5 mcg./cc.

Equal quantities (by weight) of tetracycline and oxytetracycline inhibited two strains of *E. histolytica* in 31.25 mcg./cc. and three strains in 15.625 mcg./cc.; whereas tetracycline or oxytetracycline alone inhibited three strains in 125 mcg./cc. and two strains in 62.5 mcg./cc. There was a fourfold increase in the inhibitory effect when

tetracycline and oxytetracycline were combined.

Equal quantities (by weight) of oxytetracycline and carbomycin inhibited three strains of *E. histolytica* in 62.5 mcg./cc. and two strains in 15.625 mcg./cc. while oxytetracycline alone inhibited four strains in 125 mcg./cc. and one strain in 31.25 mcg./cc., indicating that there was a twofold increase in the inhibitory effect when oxytetracycline was combined with carbomycin.

Equal quantities (by weight) of tetracycline and carbomycin inhibited one strain of *E. histolytica* in 125 mcg./cc., two strains in 62.5 mcg./cc. and one strain in 15.625 mcg./cc., whereas tetracycline alone inhibited one strain in 250 mcg./cc., two strains in 125 mcg./cc. and one strain in 62.5 mcg./cc., indicating that there was a twofold increase in the inhibitory effect on three strains and a fourfold increase on one strain.

It may be possible to potentiate the therapeutic action of oxytetracycline, tetracycline and carbomycin by combining tetracycline with oxytetracycline, and oxytetracycline or tetracycline with carbomycin.

Summary and Conclusion. Oxytetracycline inhibited six strains of *E. histolytica* in a concentration of 31.25 to 250 mcg./cc., while tetracycline inhibited the same strains in 62.5 to 250 mcg./cc.

There was a fourfold increase in the inhibitory effect on cultures of *E. histolytica* when equal amounts (by weight) of tetracycline and oxytetracycline were combined, and a twofold increase when tetracycline or oxytetracycline were combined with carbomycin.

TABLE 3.—THE EFFECT OF OXYTETRACYCLINE, TETRACYCLINE, AND EQUAL CONCENTRATIONS OF OXYTETRACYCLINE AND TETRACYCLINE ON CULTURES OF ENDAMEBA HISTOLYTICA

Strains of E. histolytica	*Mcg./cc.*								
	1,000	*500*	*250*	*125*	*62.5*	*31.25*	*15.625*	*7.81*	*Control*
					Oxytetracycline				
Columbia	−	−	−	−	−	+	+	+	+
Gloria	−	−	−	−	+	+	+	+	+
Korea	−	−	−	−	+	+	+	+	+
E. histolytica with *E. coli*	−	−	−	−	−	+	+	+	+
E. histolytica with *Cl. perfringens*	−	−	−	−	+	+	+	+	+
					Tetracycline				
Columbia	−	−	−	−	−	+	+	+	+
Gloria	−	−	−	−	+	+	+	+	+
Korea	−	−	−	−	+	+	+	+	+
E. histolytica with *E. coli*	−	−	−	−	−	+	+	+	+
E. histolytica with *Cl. perfringens*	−	−	−	−	+	+	+	+	+
					Oxytetracycline plus Tetracycline				
Columbia	−	−	−	−	−	−	+	+	+
Gloria	−	−	−	−	−	−	−	+	+
Korea	−	−	−	−	−	−	+	+	+
E. histolytica with *E. coli*	−	−	−	−	−	−	−	+	+
E. histolytica with *Cl. perfringens*	−	−	−	−	−	−	−	+	+

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RESERPINE (SERPASIL) IN THE TREATMENT OF HYPERTENSION*

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Preliminary observations have indicated that the whole root of *Rauwolfia serpentina* and some of its extracts are effective therapeutic agents[2,4,10,11,12] for the treatment of mild to moderately severe hypertension. Therefore, it seems worthwhile investigating the efficacy of pure alkaloids of *Rauwolfia serpentina* in an effort to find an agent or agents which are primarily responsible for the hypotensive activity exhibited by the crude extracts. It is quite possible that some of the pure alkaloids will effectively lower the blood pressure in patients with severe hypertension, wherein the crude root is not very effective. The following report is an evaluation of reserpine (Serpasil),** a pure alkaloid of *Rauwolfia serpentina,* which has been obtained by chemical extraction but has also been chemically identified[8]. The study has been conducted on outclinic patients under circumstances quite similar to a general office practice. Observations have also been made on the acute intravenous administration of this agent to hospitalized patients.

Methods. OUTPATIENT TREATMENT OF HYPERTENSION (ORAL THERAPY). A group of 62† unselected, ambulatory patients with mild to severe hypertension were treated with oral reserpine (Serpasil) on an outpatient basis. The patients were followed at weekly or semi-weekly intervals for 4 weeks or longer before initiation of therapy. This constituted the control period during which time the patients received only placebos. All of them had blood pressure determinations of 150/100 or greater during the control periods. Following the control period, oral reserpine was started after which the patients were followed also at weekly or semi-weekly intervals as outpatients. The control as well as the follow-up blood pressure determinations were recorded by the physician (investigator) in both the supine and upright positions at the time of each clinic visit. The control blood pressures for each patient as recorded in the

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†All patients who obtained a reduction in blood pressure to normotensive ranges (less than 150/100) at any time during the control period were discarded from the study and are consequently not included in the 62 patients treated with reserpine.

current study were obtained by taking the average of all blood pressure determinations during the control period in each position. The post-drug blood pressures were determined in the same manner for 2 periods. The first period (D_1) consists of observations made during the first one to two months after initiating specific drug therapy. The second period (D_2) constitutes the observations for a period varying from 2 to 7 months of treatment. There were 62 patients followed for a period of one to two months (period D_1) after initiation of therapy, and 47 of the 62 patients were followed for 2 to 7 months (D_2).

The initial dose of reserpine was usually one to two mg. per day given orally in divided doses after each meal and at bedtime. If excessive sedation occurred the dose was temporarily decreased, and after several weeks it was again increased to the previous level. If no reduction in blood pressure was observed after 2 weeks the dose of reserpine was progressively increased until as much as 1.5 mg. were given 4 times daily (or a total of 6.0 mg. daily) to some patients in an effort to obtain maximum effectiveness with this drug. These rather large doses were chosen because the side effects were not serious or incapacitating, and excessive hypotension was not observed.

ACUTE STUDIES (INTRAVENOUS ADMINISTRATION OF RESERPINE). Seventeen unselected, hypertensive patients were given reserpine intravenously with the dose varying between 1 and 3 mg. The drug was administered in 100 cc. of 5% glucose in distilled water over a period of 15 to 30 minutes. The patients were closely observed for 5 to 6 hours thereafter with the blood pressure and pulse rate being recorded every 5 to 10 minutes in the recumbent position. Similar determinations were also made in the upright position after a significant reduction in blood pressure was observed.

Results. OUTPATIENT TREATMENT OF HYPERTENSION WITH RESERPINE ADMINISTERED ORALLY. For purposes of analysis, the 62 patients who were treated with oral reserpine have been divided into 2 groups according to the level of diastolic blood pressure. Group 1 consists of 34 patients with the most severe hypertension in whom the average diastolic pressure during the control period was more than 120 mm. Hg. Group 2 consists of 28 patients in whom the diastolic pressure was more than 100 but less than 120 mm. Hg. Sixty-two patients have been followed for one to two months (period D_1) while receiving reserpine, and 47 of the 62 patients have been followed for a period of 2 to 7 months (period D_2).

The clinical status and complications of the disease for all of the patients prior to therapy are summarized in Table 1. There were 35 women and 27 men with ages ranging from 27 to 79. About one-fourth (14) of the patients had evidence of renal impairment, which was severe in only 3 cases. The cardiac complications were mild in severity in the majority of patients. Thirteen of the patients, or about one-fifth, had developed congestive heart failure, at some time prior to therapy. This was severe in only 4 patients. Two of the patients complained of precordial pain which was typical of angina pectoris, and one had previously had a myocardial infarction. The electrocardiograms during the control period were interpreted as being abnormal in 37 patients. In 28 patients there was evidence of left ventricular hypertrophy or strain, or both and, in 9, frank myocardial damage was present.

Cerebrovascular disease was present in 20 patients, or about one-third of those observed. This was evidenced by a history of previous cerebral vascular accidents with varying degrees of residual impairment. Hypertensive encephalopathic manifestations were present in only one patient. Eye ground changes varied from Grades 1 to 3 according to the Keith-Wagener classification. Eleven of the patients had retinal hemorrhages and other changes consistent with Grade 3 retinopathy, but there were no cases classified as malignant hypertension.

The blood pressure responses of the 2 groups of patients are presented in Table 2 (A-B). The period of follow-

TABLE 1.—SUMMARY OF THE CLINICAL STATUS AND COMPLICATIONS DUE TO HYPERTENSION IN THE PATIENTS PRIOR TO RECEIVING RESERPINE THERAPY BY MOUTH

	Number Patients	Age	Sex		Race		Renal††				Functional Cardiac Classification‡‡					Cardiac Enlargement		
			M	F	W	C	0	1+	2+	3+	0	1+	2+	3+	4+	0	Mild–Mod.	Marked
Group 1*	34	52	15	19	5	29	25	4	2	3	10	14	5	4	1	10	17	7
Responsive†	20	54	8	12	3	17	16	3	0	1	8	6	3	3	0	8	7	5
Unresponsive	14	50	7	7	2	12	9	1	2	2	2	8	2	1	1	2	10	2
Group 2**	28	54	12	16	9	19	23	4	1	0	13	4	10	1	0	17	10	1
Responsive†	13	50	4	9	5	8	10	3	0	0	9	1	2	1	0	9	3	1
Unresponsive	15	58	8	7	4	11	13	1	1	0	4	3	8	0	0	8	7	0
TOTAL	62		27	35	14	48	48	8	3	3	23	18	15	5	1	27	27	8

	Electrocardiogram			Cerebral				Eye Grounds‡			
	Normal	LVH or LVS	Myocardial Damage	0	1+	2+	3+	1+	2+	3+	4+
Group 1*	11	17	6	23	4	5	2	6	19	9	0
Responsive†	8	9	3	16	2	1	1	5	12	3	0
Unresponsive	3	8	3	7	2	4	1	1	7	6	0
Group 2**	14	11	3	19	5	0	4	11	15	2	0
Responsive†	9	3	1	10	2	0	1	7	6	0	0
Unresponsive	5	8	2	9	3	0	3	4	9	2	0
TOTAL	25	28	9	42	9	5	6	17	34	11	0

Key to Abbreviations:
M = Male
F = Female
W = White
C = Colored
Mod. = Moderate
LVH = Left ventricular hypertrophy
LVS = Left ventricular strain

* Patients with diastolic blood pressure higher than 120 mm. Hg.
** Patients with diastolic blood pressure higher than 100 but lower than 120 mm. Hg.
† Patients in whom the mean blood pressure decreased more than 20 mm. Hg during therapy with oral reserpine.
‡ Keith-Wagener-Barker classification.
‡‡ The functional capacity of each patient was graded from I to IV according to the classification of the American Heart Association.

†† Classified on the basis of the severity of renal involvement:
0 = No impairment.
1+ = Impairment of renal function studies without azotemia.
2+ = Mild azotemia (BUN above 20 but below 40 mg. per 100 cc.)
3+ = Severe azotemia (BUN above 40 mg. per 100 cc.).
4+ = Uremia.

TABLE 2A.—BLOOD PRESSURE RESPONSE TO RESERPINE ADMINISTERED ORALLY TO 34 PATIENTS WITH CONTROL DIASTOLIC PRESSURES ABOVE 120 MM. HG (GROUP 1)

	Supine Blood Pressure mm. Hg						*Upright Blood Pressure mm. Hg*						*Pulse Rate*			*Reserpine Daily Dose (mg.)*		
	C		*D*$_1$		*D*$_2$		*C*		*D*$_1$		*D*$_2$							
Patient	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*C*	*D*$_1$	*D*$_2$	*D*$_1$	*D*$_2$	*Diagnosis*
1. J. J.	185	110	171	99	171	102	169	121	148	93	150	100	83	71	70	3.0	5.0	HVD
2. L. M.	176	130	179	106	163	107	176	130	176	110	152	110	105	79	77	4.0	4.0	HCVD
3. L. B.	215	133	171	105	181	112	218	135	183	112	193	115	88	58	62	3.0	6.0	HVD
4. J. H.	206	128	196	108	197	108	206	130	176	101	190	103	98	62	68	4.0	6.0	HCVD
5. C. T.	253	143	193	104	204	113	235	147	187	127	194	121	96	64	64	2.0	4.0	HCVD
6. C. J.	220	132	203	125	183	108	225	136	200	115	181	107	81	80	67	1.0	2.0	HCVD
7. E. D.	225	150	180	120	198	132	230	145	180	130	196	134	80	72	72	4.0	5.0	HCVD
8. E. M.	240	134	175	107	182	104	235	142	172	100	176	101	79	62	62	3.0	4.0	HCVD
9. E. B.	235	145	183	111	193	116	237	150	192	130	200	131	73	63	66	4.0	6.0	HCVD
10. J. P.	197	137	193	113	213	127	197	130	165	107	193	120	77	63	69	3.0	4.0	HCVD
11. I. H.	227	125	190	100	190	108	210	133	150	90	155	94	85	76	72	2.0	2.0	HVD
12. M. S.	225	125	198	107	198	103	218	130	200	103	191	100	76	60	62	2.0	2.0	HVD
13. J. R.	218	131	188	111	180	108	223	135	199	121	191	117	83	67	67	4.0	2.0	ACVD & HCVD
14. W. C.	204	145	190	111	190	113	191	150	188	120	188	120	98	82	80	4.0	4.0	HCVD
15. M. D.	248	122	220	100	208	99	230	123	210	95	202	95	97	70	71	2.0	4.0	HCVD
16. E. H.	221	138	206	124	198	124	225	140	200	125	192	122	67	64	66	4.0	4.0	HCVD & ASHD
17. P. H.	234	123	225	106	216	102	236	123	230	103	219	98	93	79	78	4.0	6.0	HCVD & ASHD
18. S. R.	186	124	174	105	172	102	182	122	173	102	172	102	86	68	72	2.0	2.0	HVD
19. E. K.	220	133	173	95			215	135	175	93			86	92	—	2.0	—	HCVD
20. C. S.	263	125	243	105			255	135	246	121			78	75	—	4.0	—	HCVD & ACVD
Mean for 20 Responsive Patients	220	132	193	108	191	110	216	135	188	110	185	111	85	70	69	3.1	4.0	
% of Control			88	82	87	83			87	81	86	82		82	81			
Mean for 14 Unresponsive Patients	218	131	216	120	216	124	211	134	207	122	209	124	83	68	66	3.1	4.7	

Key to abbreviations:
C = Control blood pressure (average of all observations during control period).
D$_1$ = Blood pressure during 2 months while receiving reserpine (average of all observations).
D$_2$ = Blood pressure during 2 to 7 months period while receiving reserpine (average of all observations).
Syst. = Systolic blood pressure.
Diast. = Diastolic blood pressure.
HVD = Hypertensive vascular disease.
HCVD = Hypertensive cardiovascular disease.
ACVD = Arteriosclerotic cardiovascular disease.
ASHD = Arteriosclerotic heart disease.

TABLE 2B.—BLOOD PRESSURE RESPONSE TO RESERPINE ADMINISTERED ORALLY TO 28 PATIENTS WITH CONTROL DIASTOLIC PRESSURES 100 TO 120 MM. HG (GROUP 2)

	Supine Blood Pressure mm. Hg						*Upright Blood Pressure mm. Hg*						*Pulse Rate*			*Reserpine Daily Dose (mg.)*		
	C		*D*$_1$		*D*$_2$		*C*		*D*$_1$		*D*$_2$							
Patient	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*Syst.*	*Diast.*	*C*	*D*$_1$	*D*$_2$	*D*$_1$	*D*$_2$	*Diagnosis*
1. F. J.	160	110	128	95	131	92	175	112	133	90	123	91	84	72	73	2.0	2.0	HVD
2. I. W.	155	104	110	70	113	71	155	106	121	85	121	81	74	47	51	2.0	2.0	HCVD
3. I. W.	200	103	174	77	173	83	180	90	175	83	173	85	82	68	63	2.0	4.0	ACVD & HCVD
4. M. S.	191	115	161	94	170	100	195	118	150	96	167	104	78	62	62	3.0	4.0	ASHD & HVD
5. B. F.	220	120	187	107	202	109	207	116	178	100	186	104	93	82	81	2.0	5.0	AVD & HVD
6. L. B.	166	110	143	95	144	93	173	118	143	99	136	94	83	74	70	3.0	3.0	HVD
7. L. M.	158	103	140	92	140	90	166	107	142	90	138	88	73	65	63	3.0	3.0	HVD
8. I. W.	184	106	173	100	174	104	186	108	168	84	169	91	79	79	80	4.0	4.0	ACVD & HCVD
9. M. D.	195	100	170	88	166	87	210	114	147	86	162	100	88	68	73	2.0	4.0	HCVD & ACVD
10. A. R.	160	100	142	72	160	92	163	103	142	72	153	83	80	60	60	2.0	2.0	HVD
11. R. K.	200	110	166	96	210	103	182	113	142	84	182	104	80	76	80	2.0	4.0	HVD
12. P. H.	213	110	186	83			205	102	185	85			79	53		4.0		HCVD & ACVD
13. B. T.	200	105	150	85			191	101	140	85			81	68		2.0		HVD
Mean for 13 Responsive Patients	185	107	156	89	162	93	184	108	151	88	155	93	81	67	69	2.5	3.4	
% of Control			84	83	88	87			82	81	84	86		83	85			
Mean for 15 Unresponsive Patients	183	109	175	101	189	103	171	110	164	100	166	102	76	65	67	2.8	3.5	

See Table 2A for key to abbreviations.

up after receiving reserpine varied from one to 7 months. The observations on blood pressure presented in Table 2 (A-B) are the average values for each patient before (control) and for the 2 periods (D_1 and D_2) after receiving therapy, one at one to 2 months (D_1) and one at 2 months or longer (D_2). The mean values but not the individual determinations for the unresponsive patients in both Groups 1 and 2 are also presented in the tables. A reduction in mean blood pressure of 20 mm. Hg or more was considered to be a significant blood pressure response to the drug. The amount of the drug required to produce maximum reduction in the blood pressure was usually 2.0 mg. daily which was administered in divided doses. Larger amounts of the drug did not appear to produce a further reduction in blood pressure nor did they appear to produce any great increase in the intensity of the side reactions. The patients in Group 1 (Table 2A) received (on an average) larger doses of the drug than the patients in Group 2 (Table 2B) as a result of a more vigorous attempt to produce further reduction in blood pressure in the patients with more severe hypertension. The increase in the average amount of drug used in the second post-drug period (D_2) as compared to period D_1 was usually not necessary to maintain a response in the patients who had previously obtained a reduction in blood pressure. Rather it was an attempt to produce a further reduction in blood pressure in some patients and obtain a response in others who previously were unresponsive.

The mean values shown in Table 2 (A–B) indicate that very little postural hypotensive effect occurred as a result of oral reserpine therapy. Of the total of 62 patients followed for a period of one to 2 months, 29 (47%) showed a significant reduction in blood pressure. Of the 47 patients followed for 2 to 7 months, 24 (51%) showed a significant response. Therefore, the incidence of blood pressure response was not increased by more prolonged treatment. There were 14 (23%) of the patients rendered normotensive (less than 150/100 mm. Hg) in the group followed for one to 2 months and 6 (13%) in the group followed for 2 to 7 months. Three of the patients who became normotensive after one to 2 months of therapy are not included in Tables 2A and 2B since they were patients with mild disease and the normotensive level of blood pressure was attained without showing a reduction in the mean blood pressure in excess of 20 mm. Hg. Seven of the patients who were normotensive after one month of treatment became mildly hypertensive with the longer period of follow-up. However, the increase in blood pressure in every instance was slight and did not represent a true escape from control. One of the 14 patients who became normotensive during period D_1 was not followed long enough to be included in period D_2. Percentagewise, as many patients with diastolic pressures above 120 mm. Hg responded (47%) after one month of therapy as did those with diastolic pressures between 100 and 120 mm. Hg (46%). However, except for 2 patients, a reduction in blood pressure to normotensive levels was obtained only in those patients with less severe disease. Although, after a longer period of follow-up, the response rate decreased from 46 to 32% in the Group 2 patients with lower diastolic pressures, this did not occur in Group 1 patients with higher diastolic pressures. In the latter instance the percent responding actually increased from 47 to 68%. The patients in this study with moderate to marked renal and cerebral impairment showed a tendency toward non-responsiveness from the standpoint of blood

TABLE 3.—SIDE REACTIONS AND SYMPTOMS IMPROVED (RESERPINE AND RAUWILOID*)

	Side Reactions					
	Reserpine				*Rauwiloid*	
	D_1		D_2		D_x	
Symptoms or Signs	*No.*	*%*	*No.*	*%*	*No.*	*%*
1. Bradycardia	44	71	33	70	33	77
2. Sedation	29	47	13	28	23	53
3. Nasal congestion	40	65	33	70	24	56
4. Sense of well-being	22	35	15	32	13	30
5. Increased bowel movements	3	5	3	6	7	16
6. Increased appetite	37	60	28	60	22	51
7. Weight gain	31	50	23	49	23	53
8. Fatigue and weakness	27	44	23	49	7	16
9. Dizziness	13	21	3	6	—	—
10. Dreams	2	3	2	4	1	2
11. Dysuria	0	0	0	0	—	—
12. Impotence	0	0	2	4	—	—
Total Treated	62	100	47	100	43	100

	Reserpine						*Rauwiloid*		
	D_1			D_2			D_x		
Symptom or Sign Improved	*Total No.*	*No. Improved*	*%*	*Total No.*	*No. Improved*	*%*	*Total No.*	*No. Improved*	*%*
1. Headache	22	16	73	15	14	93	15	9	60
2. Angina	2	1	50	2	1	50	10	6	60
3. Congestive heart failure	6	2	33	5	1	20	11	2	18
4. Cardiac enlargement	35	0	0	31	1	3	25	1	4
5. Electrocardiogram	37	2	5	28	6	21	31	0	0
6. Fundi	11	0	0	8	0	0	2	0	0
7. Renal impairment	14	0	0	10	1	10	7	0	0
8. Blood pressure	62	29	47	47	24	51	43	20	47

* Rauwiloid (Extract of *Rauwolfia serpentina* containing multiple alkaloids).
D_1 = First two months of treatment with reserpine.
D_2 = Total period of treatment varying from 2 to 7 months.
D_x = Period of treatment with Rauwiloid (average 4 months).
No. = Number
Total No. = Total number with symptom or sign due to hypertension.
No. Improved = Number improved

pressure reduction. Those with mild involvement were more responsive (Table 1). The patients with Grade 3 retinopathy showed a definite tendency toward non-responsiveness.

The side effects associated with reserpine therapy are listed in Table 3. These have been compared with those occurring during treatment with the extract, Rauwiloid.* None of the untoward effects have been serious or incapacitating. A reduction in pulse rate was observed in the majority of the patients, and this was defined as a decrease of 10 or more beats per minute when compared to the control value. The pulse rate during therapy was frequently below 60 beats per minute. The degree and frequency of slowing of the pulse rate did not decrease with the longer period of follow-up (D_2). Sedation was a common manifestation during therapy, consisting of mild to moderate drowsiness, general relaxation, and loss of initiative and "pep". The frequency and severity decreased with longer periods of observation.

The most frequent and bothersome untoward effect was nasal congestion which tended to decrease in intensity despite continued therapy, but percentagewise the incidence was just as great during the longer period of follow-up (D_2) as it was initially (D_1). An increase in appetite and significant weight gain occurred in approximately one-half of the patients throughout the period of therapy. The weight gain appeared to be a direct result of the increase in appetite. Some patients noted that the appetite returned to control status quite promptly when the drug was not taken for a few days. Fatigue and weakness were also complaints which did not decrease in frequency with more prolonged therapy, but the severity definitely decreased. Some patients commented that they felt too weak to do anything, and some mentioned weakness in the lower extremities. Mild dizziness was a complaint in about one-fifth of the patients during the first month of therapy. This was not postural. It occurred in only 3 patients after one month of continued therapy. A few patients developed an increase in frequency of bowel movements, but in every instance this was temporary and not of diarrheal proportions. Dysuria and impotence were not problems by comparison to therapy with ganglionic blocking agents.

Increase in dosage of reserpine above 2.0 mg. daily did not appear to greatly increase the incidence or severity of side effects. Comparison of the side reactions of reserpine with those of Rauwiloid, an extract of *Rauwolfia serpentina*, reveals similar findings, but they develop more rapidly following reserpine administration.

As a result of the combination of a relatively short term of post-drug follow-up and the absence of marked blood pressure reduction in many instances, the manifestations of improvement were not numerous. These are shown in Table 3 and are compared with those observed during therapy with Rauwiloid[4]. Improvement in headache occurred in the majority of patients in whom this complaint was presented. However, in many of the patients these were not frank hypertensive headaches. Angina improved in one patient who also showed a significant blood pressure response. Congestive heart failure improved in 2 patients, one of whom also had a significant blood pressure reduction. Reserpine was merely a supplementary therapeutic agent in these cases, but the regimen for the collateral thera-

*Extract of *Rauwolfia serpentina* containing multiple alkaloids. Supplied by Riker Laboratories, Incorporated, Los Angeles, California.

TABLE 4.—RESPONSE OF 17 HYPERTENSIVE PATIENTS TO RESERPINE ADMINISTERED INTRAVENOUSLY

Patient		Dose, mg.	Blood Pressure C Syst.	C Diast.	T_1 Syst.	T_1 Diast.	T_2 Syst.	T_2 Diast.	T_3 Syst.	T_3 Diast.	T_4 Syst.	T_4 Diast.	T_5 Syst.	T_5 Diast.	T_6 Syst.	T_6 Diast.	Pulse C	Pulse D	Side Effects	Diagnosis	Age	Sex	Race
1. M.D.	Supine	2.0	235	135	180	110	190	110	160	95	120	70	145	80	165	90	85	56	Somnolence, nasal congestion, and hunger	HCVD	62	F	C
	Upright						170	90			70	50	135	70	130	90							
2. M.D.	Supine	2.0	175	100	160	90	145	85	140	80			160	90			60	48	Nasal congestion, somnolence	HCVD	62	F	C
3. L. C.	Supine	2.0	260	145	250	130	200	120	190	110	190	110	200	120	210	120	84	64	Nausea and vomiting, followed by hunger, drowsiness, and nasal congestion	HCVD	47	F	C
	Upright								150	90	120	90	140	90	210	120							
4. W.C.	Supine	2.0	200	110	190	110	160	90	160	90	150	80	140	80	135	90	92	80	Mild drowsiness	HCVD	55	F	C
	Upright						160	90					130	100	160	100							
5. C. S.	Supine	2.0	250	120	250	120	215	100	230	100	220	100	200	100	—	—	80	72	None	HCVD & ACVD	76	M	C
	Upright								220	100													
6. D.D.	Supine	2.0	200	120	190	120	150	100	60	40	140	90	160	110	190	120	72	64	Moderate somnolence and excessive hypotension at 3 hours after drug given	HCVD	47	F	C
7. W.B.	Supine	2.0	180	120	140	100	140	100	135	95	130	90	—	—	—	—	64	64	Nasal congestion, mild somnolence	HVD	38	M	C
	Upright						150	110															
8. W.S.	Supine	2.0	240	160	250	160	235	130	190	120	190	130	220	150	—	—	68	68	None	HCVD	47	M	C
	Upright												210	130									
9. O.H.	Supine	1.0	205	125	180	115	180	120	165	100	150	100	150	90	150	90	72	80	Moderate drowsiness	HCVD & ACVD	68	F	C
	Upright								150	105													
10. E. S.	Supine	2.0	200	110	175	90	160	90	150	90	155	90	145	85	—	—	76	68	Somnolence, nasal congestion, hunger, "hunger cramp"	HVD	52	F	C
	Upright						150	100	Not obtainable		140	90	110	80									
11. R. L.	Supine	2.0	240	170	220	150	240	160	220	160	220	140	230	150	—	—	108	92	Mild drowsiness	HCVD	50	M	C
12. L.M.	Supine	1.0	155	100	155	100	155	105	150	90	145	96	155	100	—	—	68	60	None	HVD	46	M	W
13. W.C.	Supine	1.0	210	110	170	115	205	110	200	110	180	110	190	110	—	—	80	68	Mild drowsiness	HCVD	55	F	C
14. W.T.	Supine	2.0	190	100	190	100	190	100	180	100	180	100	180	100	—	—	68	60	None	HCVD	42	F	C
15. A.*	Supine	2.0	300	180	280	160	270	168	130	80	140	84	138	78	150	90	94	90	Marked sedation	MHCVD, uremia	32	F	C
16. C.‡	Supine	3.0	260	136	260	130	220	120	200	120	180	100	180	98	190	100	90	84	Sedation	MHCVD, Encephalopathy‡	48	M	W
17. B.	Supine	2.5	230	138	236	140	200	138	190	130	200	136	210	140	220	150	80	82	None	MHCVD	38	M	W
Mean	Supine	1.9	219	128	204	120	191	114	168	101	168	102	175	105	176	106	79	71			51		
	Upright						158	98	173	98	110	77	145	94	167	103							

Key to Abbreviations

C = Control
T_1 = One hour after drug administration
T_2 = Two hours after drug administration
T_3 = Three hours after drug administration
T_4 = Four hours after drug administration
T_5 = Five hours after drug administration
T_6 = Six hours after drug administration

Syst. = Systolic blood pressure
Diast. = Diastolic blood pressure
HCVD = Hypertensive cardiovascular disease
ACVD = Arteriosclerotic cardiovascular disease
MHCVD = Malignant hypertensive cardiovascular disease
HVD = Hypertensive vascular disease

* Similar response on 4 occasions when drug was given at 12-hour intervals. However, uremia progressed and blood pressure reduction was no longer feasible.
‡ Encephalopathy improved on this treatment for 7 days.
D = Point of maximum reduction in pulse rate.

peutic agents was not altered. Cardiac enlargement improved in only one case, and in 6 cases improvement in the electrocardiogram was observed which consisted of a reduction in the left ventricular strain pattern. No improvement in retinopathy was noted. One patient showed improvement in renal function; however, no significant blood pressure response occurred.

ACUTE STUDIES (INTRAVENOUS ADMINISTRATION OF RESERPINE). The results in the 17, unselected, hypertensive patients receiving reserpine intravenously are summarized in Table 4. Fifteen of the 17 patients were given only a single injection of the drug. One patient (No. 15) with malignant hypertension received the drug on 4 occasions at 12-hour intervals with responses similar to that shown in Table 4. However, uremia progressed and blood pressure reduction then was no longer feasible. One patient (No. 16) with malignant hypertension and encephalopathy improved on intravenous therapy with reserpine for 7 days following which she was placed on a more permanent regimen.

The response to intravenous reserpine was characterized by a lag period of one to two hours from drug administration to blood pressure reduction (Mean Supine Values, Table 4). Thirteen of the 17 patients (76%) demonstrated a significant reduction in blood pressure.* Nine of the patients (53%) became normotensive, of whom 5 had control diastolic blood pressures above 120 mm. Hg. The most marked blood pressure reduction usually occurred about 3 hours after intravenous administration. In the majority of the patients the reduction in blood pressure persisted for 5 to 6 hours after the drug was given. There was a postural effect in the patients showing the most marked blood pressure response. In one patient (No. 6 in Table 4) the blood pressure dropped excessively, and it was necessary to administer norepinephrine for about one hour before the blood pressure became stabilized at an adequate level without the support of vasoconstrictor drugs. The response to norepinephrine was rapid, and there was no evidence of adrenergic blockade. During the severe hypotensive phase, this patient was irrational, restless, and markedly lethargic.

The average dose of intravenously administered reserpine was 1.9 mg. Two patients were given 1.0 and 2.0 mg. on separate days. One of these patients was non-responsive after 1.0 mg. but responsive after 2.0 mg. The other patient developed more marked blood pressure reduction after the larger dose of the drug, indicating that greater effectiveness can be expected when larger doses are employed.

The over-all effect on pulse rate is indicated by the mean control value of 79 as compared to the lowest pulse rate value after drug administration of 71 per minute. The pulse rate decreased 10 beats or more per minute in only 5 of the patients indicating that the pulse slowing effect was not as pronounced after acute intravenous administration of reserpine as after the chronic oral administration.

The most prominent side effect was sedation as manifested by drowsiness and somnolence, being evident in 12 (70%) of the patients. Five (30%) of the patients developed mild nasal congestion, and 3 (18%) mentioned a sensation of hunger. Several patients developed conjunctival injection. These side effects were usually noted about the time of the onset of blood pressure reduction but rarely persisted for more than one to two hours. The disappearance of the somnolence usually was not accompanied by an evident in-

*Supine position.

crease in blood pressure, indicating that the sedation was probably not responsible for the blood pressure reduction. This is further supported by the patients who showed a postural blood pressure response.

Discussion. PHARMACOLOGY. The exact way in which reserpine reduces the blood pressure is not known. Both clinical and laboratory evidence seems to be in favor of a central type of action. The best clinical evidence is the absence of significant orthostatic hypotension which is a prominent component of peripherally acting agents, both ganglionic as well as adrenergic blocking agents. In the patients who obtained a rather marked reduction in blood pressure, some orthostatic effect was sometimes observed, but this was not marked. This response has also been noted with Rauwiloid[2,4].

Sedation. The drug has a prominent sedative action, but somnolence is not as prominent as in the case of barbiturates. However, if the dose of reserpine is adequate, somnolence is frequently observed. This response is usually not prominent unless the initial dose exceeds 1.0 mg. daily. After several weeks of drug administration the dose can be further increased in an incremental fashion, without producing a remarkable increase in the soporific or the sedative effects. Tolerance tends to develop to the sedation, but in a few patients it persists. When somnolence is seen, it occurs within 3 to 7 days after onset of medication, and if the drug is discontinued, it is relieved in about the same period of time. The onset of this effect is more rapid after reserpine than with the whole root extract as is its disappearance after discontinuation of therapy.

It has been suggested that the blood pressure reduction resulting from reserpine is due to its sedative properties. However, the sedative effect on our patients usually diminished or disappeared after prolonged therapy without a concomitant increase in blood pressure. Also some patients showed a significant blood pressure response without any evident sedation. Additional observations after intravenous administration of reserpine have usually shown a disappearance of sedation before blood pressure reduction has subsided.

Another suggestion has been that the Rauwolfia extracts depress the basal metabolic rate. Eight patients were studied before and after receiving Rauwiloid (which contains a high percentage of reserpine) employing basal metabolic rates and radioactive iodine uptake studies as indices of depressed metabolism. There was no significant difference between the control and post-drug observations[2].

Cardiovascular Effects. Reserpine reduces the blood pressure in the dog[1,5,9] much as it does in patients with hypertension. This response has been used by Cronheim and his associates[1] for bioassay. In this standardization, the blood pressure is measured before and after the drug has been given to dogs for 6 days. These observers found that a dose of 25 to 50 gamma per kilogram of body weight consistently reduced the blood pressure and pulse rate. This closely parallels the clinical observations that a dose of 2 mg. per day should be used if maximum effect is to be obtained when this drug is used therapeutically for the treatment of hypertension. The dose response curve to the extract Rauwiloid is apparently identical with reserpine except for the dosages employed[1].

The vasopressor response to stimulation of the central end of the vagus nerve is blocked by reserpine suggesting that vasopressor reflexes from the periphery are depressed[3,9] after medication. Furthermore, stimulation of the peripheral end of the vagus pro-

duces the typical hypotensive (parasympathomimetic) response indicating the absence of cholinergic blockade[9]. The reflexes which maintain blood pressure when changing from the supine to the upright position are not altered significantly by reserpine. As a result, orthostatic hypotension is not a major consideration. However, pressor reflexes arising above the medulla[3] and from the carotid sinus[3,7,9] are blocked by reserpine, which suggests a hypothalamic blocking action of vasopressor impulses. The bradycardia is not vagal in origin since this response is not blocked by atropine, and the pulse rate does not return to control values following atropine administered intravenously. However, there is some increase in the pulse rate, usually to a point about half way between control values and the values observed before atropine administration. This is in sharp contrast to the bradycardia which follows veratrum viride administration. When atropine is given in the latter instance, the pulse rate returns to and frequently exceeds the control values. There is no evidence to suggest that reserpine produces adrenergic blockade[9] or blockade of injected epinephrine. In fact, there is evidence that the response to epinephrine is somewhat enhanced[3] by *Rauwolfia serpentina*.

The cardiac output is not altered significantly following the administration of reserpine[5,9]. After intravenous administration of the drug, the cardiac output was quite variable and was sometimes reduced during the period of blood pressure reduction. However, these alterations were of brief duration and were usually of little consequence[5].

Gastrointestinal Effects. Diarrhea has been observed with large doses of Rauwiloid[1]. Reserpine likewise increases gastric secretion and may increase intestinal activity but not to the same degree that Rauwiloid does[1].

Renal Effects. Renal hemodynamics and electrolyte excretion rates have been studied after intravenous administration of reserpine to dogs and after intravenous and oral administration to hypertensive patients[5]. There was no significant alteration in dogs. In patients with hypertension, renal blood flow, glomerular filtration rate, and the renal excretion of water and electrolytes were not altered significantly after chronic oral administration of the drug. However, after intravenous administration glomerular filtration rate was slightly depressed at the point of maximum blood pressure reduction. There is no evidence of renal toxicity[5].

CLINICAL OBSERVATIONS. Reserpine is only moderately potent in its ability to reduce blood pressure after chronic oral administration. However, a few hypertensive patients show a marked blood pressure response with a mild to moderate postural effect when the drug is administered intravenously. The blood pressure response following both routes of administration is slow in onset (1 to 7 days orally and 1 to 3 hours intravenously). This lag period between administration and effect remains unexplained. The side effects are also slow in onset after both routes of administration and have not thus far been serious or incapacitating. They have rarely been responsible for discontinuation of therapy. Bradycardia was not observed as frequently after intravenous as after oral administration. However, the intravenous study was for the most part after single injections. Bradycardia may be more prominent after more prolonged administration. Tolerance tends to develop to the side effects from oral reserpine with the exception of bradycardia. Tolerance has not been clearly

TABLE 5.—COMPARISON OF BLOOD PRESSURE RESPONSE OF RESERPINE WITH OTHER HYPOTENSIVE DRUGS*

	No. Pts. Treated	Normotensive**		Decrease MBP >40 mm. Hg		Decrease MBP 30–40 mm. Hg		Decrease MBP 20–30 mm. Hg		Decrease MBP 20 mm. Hg	
		No.	%	No.	%	No.	%	No.	%	No.	%
Reserpine‡											
Group 1†	25	1	4	2	8	3	12	12	48	17	68
Group 2	22	5	23	0	0	2	9	5	23	7	32
Total	47	6	13	2	4	5	11	17	36	24	51
Rauwolfia (alone)[2]											
Group 1	28	3	11	4	14	3	11	2	7	9	32
Group 2	14	6	43	0	0	5	36	3	21	8	57
Total	42	9	21	4	10	8	19	5	12	17	40
Hexamethonium	58	28	48	26	45	15	26	6	10	47	81
Dibenzyline (mean for 3 groups)‡	32	14	44	15	47	3	9	3	9	21	66
Regitine (mean for 3 groups)‡	24	—	—	—	—	2	8	2	8	4	17
Anatensol (mean for 3 groups)‡	31	1	3	1	3	3	10	2	6	6	19
Veriloid (mean for 3 groups)‡	30	2	7	6	20	2	7	7	23	15	50
Apresoline (mean for 3 groups)‡	52	5	10	5	10	4	8	8	15	17	33

* Upright blood pressure.

** Blood pressure less than 150/100 in upright position.

† Group 1 = Patients with control diastolic pressure of 120 or greater.
Group 2 = Patients with control diastolic pressure of 100 to 119.

‡ Group 1 = Patients with diastolic pressure of more than 140 mm. Hg.
Group 2 = Patients with diastolic pressure of more than 120 but less than 140 mm. Hg.
Group 3 = Patients with diastolic pressure of more than 100 but less than 120 mm. Hg.

MBP = Mean blood pressure = diastolic plus $\frac{1}{3}$ of the pulse pressure.

[2] See Bibliography (reference 2).

‡ Results of oral reserpine therapy in patients receiving drug for 2 to 7 months.

% = Per cent of Number of Patients Treated.

demonstrated thus far as to the effect on blood pressure reduction.

As a result of slow onset of effects, both beneficial and untoward, and the absence of incapacitating side effects, dosage titration is difficult. It appears from this study, however, that blood pressure reduction is not increased by incremental increases in doses of reserpine orally above 2.0 mg. daily. Intravenously, it is possible that doses above 2.0 and 3.0 mg. may produce more marked blood pressure reduction than were noted here with doses of 1 to 3 mg. This requires further investigation.

Table 5 compares reserpine with other agents which are used for reducing the blood pressure in patients with hypertension. The adrenergic and ganglionic blocking agents are much more potent in this respect. However, the incidence and severity of side effects are correspondingly greater. The results with reserpine are comparable with those obtained with the other centrally acting agents such as hydralazine and veratrum derivatives, but again the toxic side effects are less prominent and not incapacitating. The results are also comparable with those obtained with extracts of *Rauwolfia serpentina* (Rauwiloid) containing multiple alkaloids. However, the onset of blood pressure reduction and side effects is notably more rapid following reserpine administration.

Summary and Conclusions. 1. Sixty-two patients with hypertension have been treated with reserpine as out-clinic patients for one to 7 months. The patients were divided into 2 groups namely, those with control diastolic arterial blood pressures between 100 and 120 mm. Hg and those with diastolic pressures in excess of 120 mm. Hg.

2. Approximately half of the patients treated obtained a significant reduction in blood pressure. All but 2 of the patients who became normotensive were from the group of patients with less severe disease. The patients who were treated for one to 2 months obtained equally as good results as those who received the drug for 2 to 7 months. There were no serious side reactions observed.

3. Doses of one to 3 mg. of reserpine were administered intravenously to 17 patients. Thirteen of these patients demonstrated a significant reduction in blood pressure about 1 to 4 hours after administration of the drug and half of them became normotensive.

4. Reserpine appears to lower the blood pressure through actions other than those related to its sedative properties.

5. There is little difference between reserpine and extracts of *Rauwolfia serpentina* containing multiple alkaloids when compared as to side reactions and blood pressure reduction in patients with hypertension.

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OBSERVATIONS ON THE METABOLIC TRANSFORMATION AND EFFECTS OF PHENYLBUTAZONE IN SUBJECTS WITH HEPATIC DISEASE

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Phenylbutazone is a potent antirheumatic agent which is capable of producing several undesirable side effects. Little is known about the factors that determine which of a group of individuals will develop an undesirable reaction to the drug. The possible role of disturbed liver function in altering the physiologic disposition, and therefore the response to phenylbutazone, has not been investigated. Conversely, little is known about the influence of phenylbutazone on liver function, in spite of the wide clinical use of the drug. The problem is accentuated by conflicting reports concerning the frequency of disturbed liver function in arthritic subjects prior to medication[9]. This paper describes some observations in patients with liver disease to whom phenylbutazone was administered. Two factors were studied: 1) The rates of biotransformation of the drug in subjects with advanced liver disease as compared to the normal. 2) The influence of long-term phenylbutazone therapy on liver function in subjects with pre-existing hepatic disease.

Methods: Phenylbutazone plasma concentrations were measured by the method of Burns *et al.*[3]. Liver function tests were performed by standard laboratory methods. These include: cephalin flocculation[5], thymol turbidity[11], serum albumin and globulin[7], serum bilirubin (total, direct immediate, and direct delayed)[4], plasma prothrombin time, whole and 12.5% saline diluted[8], alkaline phosphatase[6], bromsulfophthalein retention[10], serum cholesterol[1].

Results. 1) comparison of rates of biotransformation. Ten normal subjects (average weight, 142 lbs.) and 11 subjects with clear-cut clinical and laboratory evidence of advanced Laennec's cirrhosis (average weight, 155 lbs.) were given a single oral 800-mg. dose of phenylbutazone*, and the drug plasma levels were determined at various times over a period of 6 days. Previously reported data indicated that phenylbutazone is rapidly and completely absorbed from the gastrointestinal tract[2]. In all individuals in both groups the peak plasma level was reached in about 2 hours, and the subsequent fall of plasma concentration in each subject was at a constant rate. The rate of fall in each subject was calculated by the same method as described previously[3]. Table 1 summarizes the results. The rate of fall of plasma levels was somewhat faster in

*Phenylbutazone was administered in capsules containing 200 mg. of drug, supplied through the courtesy of Geigy Pharmaceuticals, New York, N. Y.

the cirrhotic group. Statistical analysis, however, indicated that the probability of the difference being significant is only 0.5; that is, there is one chance in two that the difference noted is due to chance alone.

2) THE EFFECT OF LONG-TERM PHENYLBUTAZONE ON LIVER FUNCTION IN PATIENTS WITH CIRRHOSIS. Nine patients with Laennec's cirrhosis were selected for this study. Patients with frank ascites were excluded because of the sodium and water retention which may accompany repeated administration of phenylbutazone. Subjects with markedly impaired liver function tests were also excluded, since it would be very difficult to detect any possible adverse influence of the experimental factor. However, all subjects included in the study presented a well documented history including physical and laboratory findings which clearly indicated the diagnosis of cirrhosis. In 3 subjects the diagnosis had been further confirmed by liver biopsy. Liver function tests were repeated every other week for a control period of at least one month, and for the duration of the study.

Phenylbutazone was administered in doses of 400 to 800 mg. per day so that a plasma level of about 100 mg. per liter was maintained for 5 months in 4 patients, and for a minimum of 1 month in the others. The relationship of plasma level to dose during maintenance therapy was not significantly different from that previously noted in subjects without liver disease[2]. The administration of phenylbutazone was interrupted in one subject because of excessive gain in weight due to fluid retention, and in a second subject because of hematemesis related to esophageal varices. In none of the patients was there any significant change in any of the liver function tests during the period of observation. Table 2 presents the initial and final liver function test values of the 4 subjects who received phenylbutazone for 5 months. It should be noted that all the above subjects had at one time or another been shown to have severe liver disease, although some of them at present do not show disturbed liver function.

TABLE 1.—COMPARISON OF THE DISPOSITION OF A SINGLE DOSE (800 MG.) OF PHENYLBUTAZONE IN SUBJECTS WITH ADVANCED LIVER DISEASE AS COMPARED TO NORMAL INDIVIDUALS

Rate of Disappearance of Phenylbutazone from Plasma			
Normal Subjects		*Cirrhotic Subjects*	
Patient	*Rate (% per day)*	*Patient*	*Rate (% per day)*
Pr	15	Mo	14
Kr	20	Carr	25
Sc	14	To	34
Lo	12	Can	26
Ch	20	Cl	39
Va	20	Ma	17
Kr	31	Be	22
Cl	29	Mx	25
Be	21	Ke	41
Mc	26	Carn	40
		Fr	24
Average	21.0		27.9
Standard Deviation	6.1		9.2

Discussion. The liver is the major site of biotransformation of many drugs.

The physiologic disposition of these drugs may, therefore, be expected to be altered by severe liver disease. In man, no significant amounts of phenylbutazone appear in the urine, although several as yet unidentified metabolites of the drug have been isolated. Preliminary results of *in vitro* experiments in our laboratory using tissue slices and homogenates indicate that the liver is probably the major site of metabolism of phenylbutazone. If liver disease blocked an important metabolic route, one would expect the rate of disappearance of phenylbutazone to be slower in subjects with severe cirrhosis. The data presented in the first portion of this communication fail to demonstrate any slowing of the rate of biotransformation of phenylbutazone by subjects with advanced Laennec's cirrhosis.

The small group studied could hardly be expected to prove or disprove the existence of rare instances of drug sensitivity resulting in liver disturbances. However, if phenylbutazone had any significant hepatotoxic action it presumably would be demonstrable in this selected group of cirrhotic subjects. None of the liver function tests showed a significant change for the worse in these patients maintained on phenylbutazone therapy.

Summary. 1) The rate of biotransformation of phenylbutazone by 10 patients with far-advanced cirrhosis was not found to be significantly different from that of normal subjects.

2) In 9 cirrhotic patients maintained on phenylbutazone therapy for 1 to 5 months, there was no evidence of further impairment of liver function.

Conclusion. Severe cirrhosis does not significantly alter the rate of phenylbutazone biotransformation. The experiments reported here show no evidence of any hepatotoxic effects due to phenylbutazone.

TABLE 2.—COMPARISON OF LIVER FUNCTION TESTS IN 4 SUBJECTS BEFORE AND IMMEDIATELY AFTER A 5-MONTH PERIOD OF CONTINUOUS PHENYLBUTAZONE THERAPY

	Subject 1		*Subject 2*		*Subject 3*		*Subject 4*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Ceph. Floc.	2+	2+	2+	0	3+	4+	0	0
B.S.P.	24	12	10	9	20	12	4	2
Thymol Turb.	0.8	1.2	9.4	9.8	12	7	1.7	1.4
A/G Ratio	4.4/3.0	4.5/2.4	4.8/2.5	4.6/2.1	3.1/4.8	3.9/3.8	2.7/2.8	5.0/2.3
Cholesterol	244	245	330	323	204	163	202	231
Alk. Phos. K.A. Units	9.4	7.1	10.5	15.9	9.0	8.5	12.6	11.8
Proth. Time								
Whole	16	15	15	15	18	18	18	14
Diluted	36	35	34	35	37	38	42	37
Bilirubin	0.8	0.45	0.4	0.5	0.5	0.4	0.34	0.35

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THE USE OF RADIOACTIVE SODIUM CHROMATE TO EVALUATE THE LIFE SPAN OF THE RED BLOOD CELL IN HEALTH AND CERTAIN HEMATOLOGIC DISORDERS*

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During the past decade information regarding the life span of red blood cells has been widely used in the evaluation of hemolytic anemias[1-8]. Most studies have been made with the Ashby technique utilizing differential agglutination to determine the survival of transfused red cells in the recipient. Much information has been gained from this procedure, especially in the understanding of pathology and therapy in patients with acquired hemolytic anemias. This method will continue to be of great value clinically when one can anticipate that the red cells of the donor and recipient will follow the same physiologic changes. However, this procedure is of limited value in evaluating the life span of red cells in those patients with red cell defects in which the donor red cells do not acquire the same abnormalities. Abnormal red cells of such patients have been transfused into normal recipients to demonstrate shortened red cell survivals. However, in some instances an adequate volume of red cells is difficult to obtain from anemic patients for this procedure, or recipients such as infants or small children have been used to obtain an adequate percentage of transfused red cells for accurate counting by the differential agglutination technique.

Studies using radioactive sodium chromate ($Na_2Cr^{51}O_4$) for the determination of red cell volume measurements have shown that this isotope remains attached to the erythrocyte for a considerable period of time[4]. This experience suggested that this technique might be applied to the measurement of red cell life span utilizing the patient's own red cells. To investigate this possibility an examination was made of the rate at which Cr^{51} labelled red cells disappear from the circulation in healthy volunteers and in patients with various hematologic disorders. In some instances the survival of Cr^{51}

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tagged red cells has been compared with simultaneous Ashby studies. Since this study was completed similar results have been reported from other laboratories[3,9].

Methods and Material. 1. PREPARATION OF RED CELLS. The technique of withdrawing, labeling and reinjecting the blood was essentially the same as that described previously[10]. The patient's blood was incubated with less than 10 micrograms of chromium per cc. of red blood cells containing approximately 100 microcuries of Cr^{51} activity. Usually 30 cc. of whole blood was withdrawn into the plastic bag with heparin as the anticoagulant. The blood was incubated with the sodium chromate tracer at room temperature for one-half hour and, after the addition of 50 mg. ascorbic acid, was reinjected. The red cell volume determination was done on some of the patients[10]. The initial specimen was collected from the recipient one-half hour after injection of the tagged red cells and further samples were collected from the patient either until the radioactivity had disappeared or it was not feasible to follow the patient longer. Radioactivity was measured in a scintillation counter. The results were expressed as counts per minute per cc. of whole blood corrected for decay to zero time. These values have been expressed as a percentage of the initial Cr^{51} value obtained one-half hour after the tagged red cell sample was infused.

The life span of transfused red cells was determined in 3 normal volunteers concurrently with the Cr^{51} tagged red cells and Ashby differential agglutination. Whole blood was obtained from normal Group O donors in 500 cc. plastic bags. The sodium chromate was introduced into the plastic bag and the whole blood was allowed to incubate for one-half hour. Ascorbic acid was added to the whole blood and the plastic bag was centrifuged to remove plasma, and the red cell mass was given to blood Group A recipients over a one-hour period. Differential agglutination was done by a modification of the method of Young *et al.*[11].

2. HEMATOLOGIC STUDIES. Laboratory procedures outlined by Ham were used for diagnosis[5]. The patients with congenital hemolytic anemia had associated siblings with this disease, and showed the diagnostic changes in the osmotic and mechanical fragilities of red cells when sterile samples of defibrinated blood were incubated for 24 hours at 37° C. The clinical diagnosis of myeloid metaplasia was confirmed in all instances by myelofibrosis of the bone marrow as well as the associated leukoerythroblastic peripheral blood findings. The patients with hypoplastic anemia had hypoplasia of all bone marrow components as determined by surgical trephine biopsies as well as pancytopenia of the peripheral blood. The diagnoses of thalassemia minor and lymphatic leukemia were made by clinical, bone marrow, and peripheral blood studies.

Results. NORMAL RECIPIENTS. Five normal male volunteers had their red cells tagged with Cr^{51} and the radioactivity of the blood was followed for approximately 100 days. One may observe in Fig. 1 the exponential loss of radioactivity during this period of study. A mean curve of these 5 studies has been constructed for comparison with other cases. It represents the disappearance of Cr^{51} from the red cell fraction of whole blood. However, the venous hematocrit measurement remained constant within a range of $\pm$ 1.3%. Hence the curve for whole blood is similar. When these results are plotted on semilogarithmic coordinates a linear function is obtained (Fig. 2). The linear loss of Cr^{51} activity is reproducible over the time interval in which 50% of the radioactivity has disappeared. For this reason, the half-life of the tagged cells has been used for purposes of comparison in the clinical studies as the time when 50% of Cr^{51} activity has disappeared from the tagged red cells. The mean half-life of the Cr^{51} tagged red cells in these 5 normal recipients was 26 days with a range from 23 to 30 days.

Three normal recipients had survival studies of chromium tagged red cells and Ashby differential agglutination studies done simultaneously*. The

*Dr. John G. Gibson performed the Ashby differential agglutination studies and generously furnished the data for these observations.

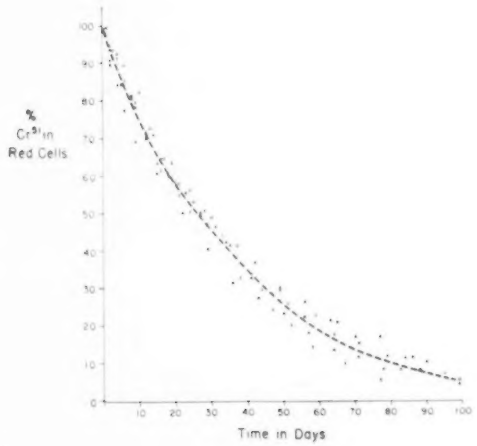

Fig. 1.—The survival of Cr^{51} tagged red cells in 5 healthy adult males. The initial percentage value of Cr^{51} is determined one-half hour after reinjection of the tagged red cells. A mean disappearance curve of Cr^{51} activity has been drawn through the plotted values.

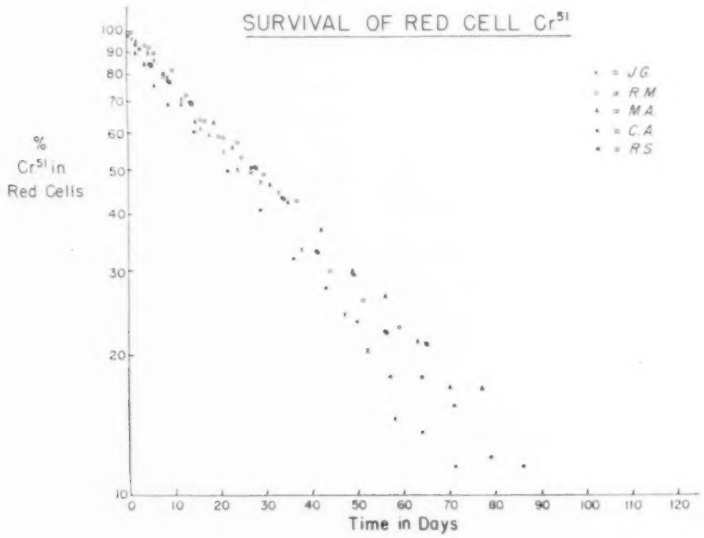

Fig. 2.—Same adult male subjects as charted in Fig. 1. The percentage of Cr^{51} activity of the tagged red cells is plotted on semilogarithmic scale. The identification of each subject has the same symbol in Figs. 1 and 2.

Ashby curves were followed over an 80- to 90-day period. By extension of the mean Ashby curve, a normal life span for the red cells of 110 days was obtained. The mean half-life of the chromium tagged cell curves was 32.5 days (Fig. 3). This half-life value is slightly higher than the results obtained above when the volunteers own red cells were tagged.

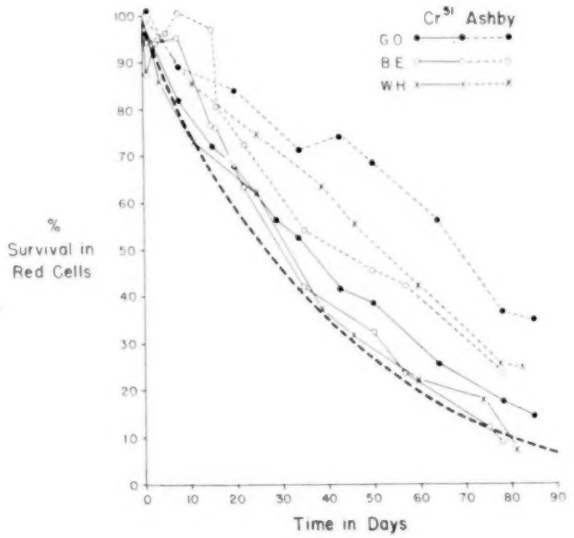

Fig. 3.—The survival of Cr^{51} tagged normal donor red cells followed concurrently by Ashby differential agglutination in 3 normal male recipients for an 80- to 90-day period. The percentage values plotted represent Cr^{51} activity and unagglutinated red cells in whole blood. The heavy dotted line is the same mean curve of the 5 adult males plotted in Fig. 1 for comparison.

The mean half-time for the elution of Cr^{51} from the red cell in the 3 recipients in which Ashby studies were done was calculated from the following formula:

$$\frac{1}{T_E} = \frac{1}{Tc} - \frac{1}{T_A}$$

Where T_E = elution half-life of Cr^{51}; Tc = observed Cr^{51} half-life and T_A = observed half-life of red cells by the Ashby technique. The formula was solved utilizing a mean half-life of Ashby survival of 55 days and mean half-life Cr^{51} value of 32.5 days for Tc. A value of 79 days for the half-life elution of Cr^{51} was obtained. This is comparable to the previously reported results[3,9].

CLINICAL STUDIES. Table 1 summarizes certain clinical data of the patients studied with hematological disorders. Patients are categorized as to specific diagnosis for discussion of the results obtained.

CONGENITAL HEMOLYTIC ANEMIA*. Four patients with this disease were studied before and after splenectomy. No patient had experienced a hemolytic crisis prior to study, and they

*We are indebted to Drs. L. K. Diamond and Doris Howell for their cooperation in these studies.

maintained constant hematocrit values during the period of observation (Table 1). Patients were not studied for at least 10 days after splenectomy[2]. There was a marked increase in the disappearance of the patients' tagged chromium cells prior to splenectomy. The mean half-life in 3 patients was 11.5 days, while in the other patient it was 19 days. All patients had normal peripheral blood values after splenectomy and the mean half-life span of the chromium tagged red cells was of 30.5 days (Fig. 4).

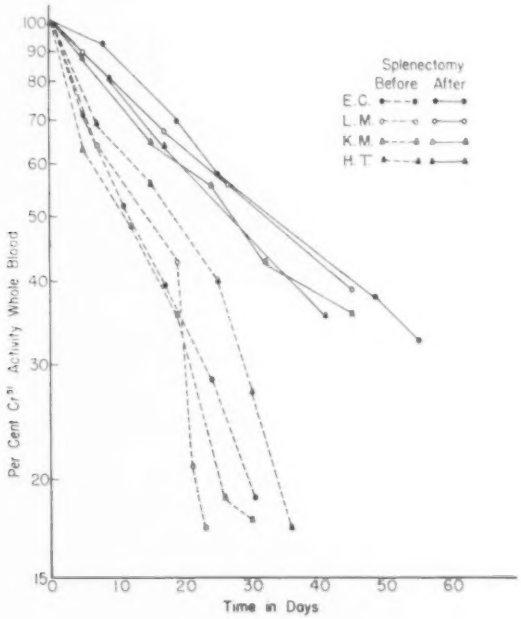

Fig. 4.—Congenital Hemolytic Anemia. Survival of Cr^{51} tagged red cells before and after splenectomy. The percentage of Cr^{51} activity is plotted on semilogarithmic coordinates in the figure and all following studies.

MYELOID METAPLASIA. Three patients were studied, two before and all of them after splenectomy. Patient F. M. was followed only for a short period before surgery because severe epistaxis from thrombocytopenia necessitated multiple transfusions. Both patients J. D. and F. M. showed a shortened Cr^{51} survival preoperatively but had no evidence of this increased hemolysis after splenectomy as can be observed in Fig. 5. The red cells in patient W. E. had a slightly decreased half-life, and this patient was not able to maintain adequate peripheral blood values with this slightly accelerated rate of blood destruction. Ashby studies done in patients F. M. and W. E. before splenectomy were in agreement with these observations, although they were not done concurrently with the chromium measurements.

THALASSEMIA MINOR. Only one study was made in this disease. The patient had a long history of marked splenomegaly associated with abdominal discomfort. Splenectomy was performed in association with a cholecys-

TABLE 1.—DETAILS OF PATIENTS WITH ANEMIA

Case	Diagnosis	Patient		Sex	Age	Weight kg.	R.B.C. Volume cc.	Half-life Cr^{51} RBC Days	Hematocrit % in Days After Injection of Sodium Chromate							
									0	1–10	11–20	21–30	31–40	41–50	51–60	61–70
1	Hypoplastic Anemia	L. E.		F	63	62.4	1035	(26)**	34.5	34.5	30.5	24				
2	" "	V. W.		F	13	36.4	—	25	34.5	33	25.5	22	18.5			
3	" "	F. P.	(lymphatic-leukemia)	M	54	71	1385	21.5	34.5	34	31.5	29	24			
4	Congenital Hemolytic Anemia	E. C.	presplenectomy	M	37	60.5	1727	12	40	40	38	38.5	38.5			
			postsplenectomy			60	2075	33	47	50	48	48	48	48		
5	" "	K. M.	presplenectomy	F	32	50	1172	11	33.5	39.5	38.5	39.5	37			
			postsplenectomy			50	—	27.5	43.5	42	44.5	45.5	48	48.5		
6	" "	L. M.	presplenectomy	F	14	63.5	—	14	29.5	30	27.5	26.5				
			postsplenectomy			63.2	—	32	36	39	40	42	42	42	44	
7	" "	H. T.	presplenectomy	F	25	63.7	1722	18	37.5	38	38	38	35			
			postsplenectomy			63	—	27.5	45.5	46	45		48		48	
8	Myeloid Metaplasia	J. D.	presplenectomy	M	72	69.2	868	6	15.5	17						
			postsplenectomy			68.2	2071	32	36	36.5	34	30.5	27.5	26.5	22.5	22
9	" "	F. M.	presplenectomy	M	54	70	1269	(12)	20.5	21						
			postsplenectomy			65.2	1910	30.5	33.5	34	34	31.5	31	29.5		29
10	" "	W. E.	postsplenectomy	F	63	61.5	989	23	29		28		27	24.5		
11	Thalassemia	A. P.	presplenectomy	M	40	64	—	15.5	36	36	34.5	35	36	37.5		
			postsplenectomy			62	—	25	49	48	42	41.5	41	40		
12	Acq. Hem. Anemia Idiopathic	W. O.	before cortisone	F	65	61	—	7	25	28.5	31					
			during cortisone 200 mg./day			61	—	10	28.5	29	29.5					
13	Acq. Hem. Anemia	B. E.*	(lymphatic-leukemia)	M	64	57	1191	2.5	28.5	26.5	falling to 14 in 5 days					
14	Uremia	F. U.		F	42	55.6	712	23	26	23	25.5	24	25.5	27		

* All red blood cell studies listed were done with patients' red cells except Case 13 in which Cr^{51} half-life was determined with tagged normal donor red cells transfused for study of Ashby survival.

** Figures in parentheses represent estimated half-life of Cr^{51} red cells inasmuch as determinations could not be made over an adequate length of time.

tectomy for pigment stones. The diagnosis of a Cooley's trait had been made before survival study was performed. One would conclude that his splenectomy was an aid in controlling blood destruction, for the half-time survival period of tagged red cells increased from 15 to 25 days following surgery (Fig. 6).

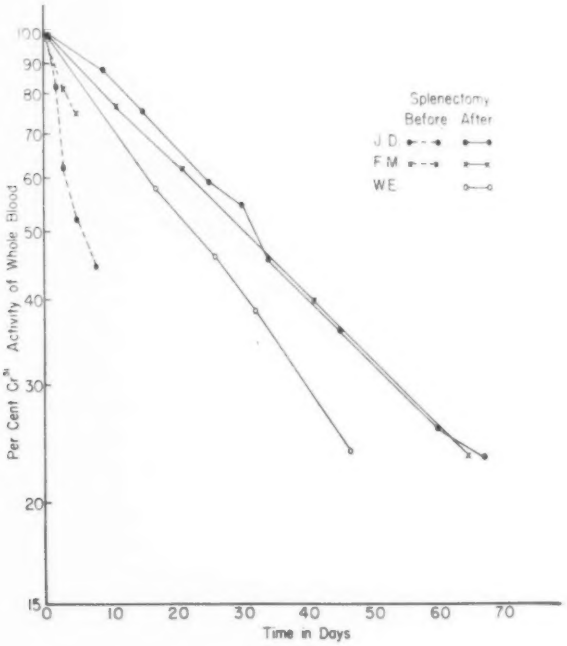

Fig. 5.—The survival of Cr^{51} tagged red cells of 3 cases of myeloid metaplasia. In 2 patients studied before splenectomy the initial disappearance rates were exceptionally rapid but after operation they were considered normal. One patient, W. E., studied 6 months postoperatively had half-life survival of 23 days to suggest a slight increase in rate of red cell destruction.

HYPOPLASTIC ANEMIA. Two patients, L. E. and V. W., with a long history of this disorder were studied by this technique. Both had received numerous transfusions. The length of time that red cell survival could be followed was limited by the need for additional transfusions. In essence, tagged red cells do not represent cells of the recipient but rather those red cells surviving from previous transfusions. By extrapolation of the disappearance curves, these patients' erythrocytes had a half-life survival of 26 and 25 days. The third patient F. P. had severe hypoplasia of the bone marrow at the time these survival studies were performed. A half-life of her red cells was 21.5 days (Fig. 7). This period was shorter than observed in other patients. Six months later the patient developed lymphatic leukemia associated with increased red cell destruction. This case is classified as hypoplastic anemia because no other diagnosis could be made at the time when the Cr^{51} survival study was done.

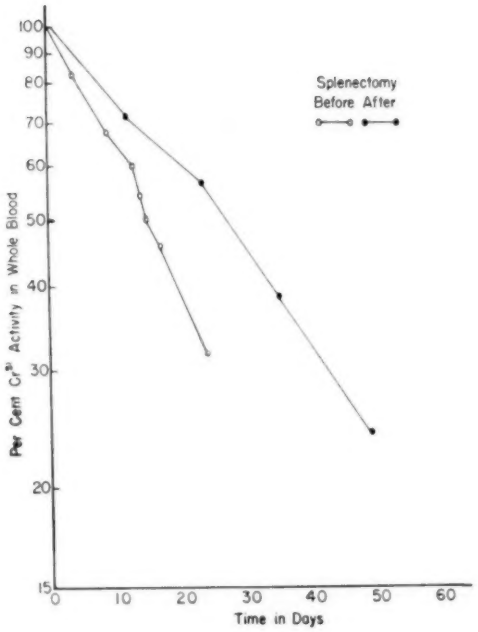

Fig. 6.—A study of a patient with thalassemia minor before and after splenectomy. The half-life of the Cr^{51} tagged red cells initially was decreased. Following splenectomy the red cell survival is normal with a Cr^{51} half-life of the red cell of 33 days.

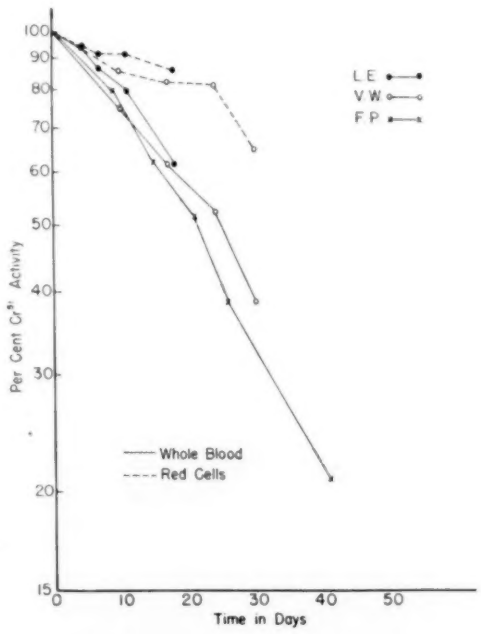

Fig. 7.—Hypoplastic Anemia. The Cr^{51} activity of whole blood suggests a normal red cell survival in patients L. E. and V. W. Patient F. P. eventually was diagnosed as lymphatic leukemia. The Cr^{51} activity of the tagged red cells in this case may suggest increased blood destruction. Two patients have the Cr^{51} activity of the red cells plotted to compare with the radioactivity of whole blood. See text.

In retrospect, her underlying disease probably accounted for the shortened Cr^{51} half-life of her red cells.

ACQUIRED HEMOLYTIC ANEMIA. Two patients with severe hemolysis were observed. Patient B. E. had chronic lymphatic leukemia with rapid blood destruction and positive Coombs' test. A concurrent chromium survival was evaluate the changes in blood destruction. The half-life of the tagged red cells increased from 7 to 10 days.

One patient with uremia and anemia was studied. The half-life of the Cr^{51} tagged red cells was 23 days. Although this value is slightly lower than the mean half-life observed in normal volunteers, the change is slight to suggest

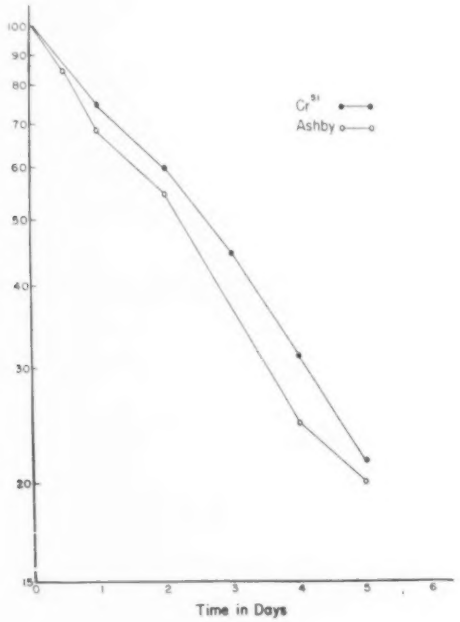

Fig. 8.—Acquired hemolytic anemia associated with chronic lymphatic leukemia. A comparison of normal donor Cr^{51} tagged red cells followed concurrently by Ashby differential agglutination in a patient. The ordinate represents the percentage of Cr^{51} activity and unagglutinated red cells plotted on semilogarithmic scale. Red cell destruction was rapid with a 50% Ashby survival of about 2 days and half-life of the Cr^{51} tagged red cells between 2 and 3 days.

compared with an Ashby survival over a 6-day period. The donor blood was prepared in the same manner in which Ashby and chromium studies were done in normal recipients as noted previously. As can be seen in Fig. 8 there is good agreement of the 2 procedures over the short time interval. Patient W. O. was followed before and after large oral doses of cortisone acetate to that the anemia is associated with impaired erythropoiesis rather than increased red cell destruction. However, no final conclusion can be made from this study.

Discussion. A reproducible pattern of red cell survival can be obtained in normal volunteers whose red cells have been tagged with radioactive sodium chromate. An exponential decline

in radioactivity coexists with a normal linear survival as measured by the Ashby technique. These characteristics constitute indirect evidence against both reutilization of Cr^{51} by red cells and the preferential tagging of a selected age group. The disparity between the Ashby and Cr^{51} curves has been attributed to elution of chromium from the red cells. Necheles *et al.*[9] calculated from their *in vitro* studies that Cr^{51} leaves the cells at an exponential rate of about 1% per day. These results are similar to the observations of Ebaugh *et al.*[3]. The data obtained in the present study of 3 volunteers is in substantial agreement and indicates a half-life of 79 days for the elution of Cr^{51}.

The mean half-life for the red cells of 5 normal male volunteers was 26 days. This period is shorter than the mean half-life of 32 days that Necheles *et al.*[9] observed in 5 studies. These differences cannot be explained at the present time, but the more gentle manipulation of the red cells by the plastic bag technique may preserve older tagged red cells which would disappear more rapidly from the circulation.

The progressive elution of radioactivity over a 75- to 80-day period coupled with the safe dosage requirements makes it difficult to obtain accurate data concerning old red cells. For that reason the time at which 50% of the initial amount of radioactivity remains (half-life) has been selected to express variations in different red cell life spans. This expression is not completely satisfactory as in some disorders a strictly exponential disappearance curve is not obtained.

The chief factor leading to the steady reduction in the percentage of Cr^{51} present in unit volume of red cells or whole blood is undoubtedly the entry of newly formed red cells into the circulation and the consequent dilution of the labelled cells. In normal subjects the hematocrit and the red cell volume remains approximately constant. In complete aplasia of the marrow no dilution of the labelled cells with new red cells would occur. Therefore, provided no differential destruction of labelled cells occurred the disappearance curve would be relatively horizontal aside from the elution of Cr^{51}, as long as there were red cells left to count. In such circumstances the red cell mass and hematocrit would be falling steadily and the absolute amount of Cr^{51} in the blood would consequently be reduced. However, the amount of Cr^{51} per unit volume of red cells would remain constant aside from the daily 1% elution. Such a hypothetical situation probably never arises but is approached by the hypoplastic anemias (Fig. 7). In these disorders the red cell disappearance curves are found to be flatter than normal. The lack of information regarding the exact number of new cells being produced makes it impossible to determine how much the decline from the horizontal is due to elution, dilution, or other factors. In these patients the hematocrit and red cell volume are low and thus any new cells being produced enter a small pool and have a greater diluting effect. This factor becomes progressively more marked as the hematocrit falls and probably accounts for the steeper slopes seen towards the end of the study. A more accurate appreciation of the rate of Cr^{51} decline thus can be obtained from the fall in whole blood Cr^{51} concentrations.

Previous studies have intimated that red cells from patients with congenital hemolytic anemia show a shorter than normal life span when transfused into normal individuals. These observations were made on recipients with intact spleens. Thus Loutit and Mollison[7] have reported, using the Ashby method, half-lives of

4, 13, and 15 days. If Cr^{51} is eluted from these red cells in the same manner as in the normal red cell, it is possible to use the previously described calculation to predict the Cr^{51} survival. A mean Ashby 50% survival of 10.6 days has been taken from Loutit's 3 studies.

Therefore,

$$\frac{1}{Tc} = \frac{1}{10.6} + \frac{1}{79} \qquad Tc = 9.3$$

An expected Cr^{51} half-life of 9.3 days is obtained. If one excludes from Loutit's study the lowest value of 4 days then the predicted Cr^{51} half-life becomes 11.8 days. Three of the 4 patients with congenital jaundice studied with Cr^{51} showed a shortened red cell survival with a half-life of 11.5 days. This value compares favorably with the above prediction. After splenectomy all patients had a normal type of Cr^{51} tagged red cell survival with a half-life of 30.5 days. These studies indicate that the red cell survives normally in the patient with congenital hemolytic jaundice after splenectomy. The normal Cr^{51} survival curves suggest that the rate of Cr^{51} elution from normal and the abnormal red cells in this disorder is essentially equal.

Similar observations were made in myeloid metaplasia. Clinically these patients showed rapid destruction of red cells and required frequent transfusions. In 2 patients (F. M. and W. E.) shortened red cell survivals had been demonstrated by Ashby studies before splenectomy. The Cr^{51} studies indicate (Fig. 5) that the abnormal red cell seen in this disorder with its marked variation in size and shape also has a shortened survival period. A normal type of Cr^{51} survival was seen in 2 patients after splenectomy. However, one other patient, W. E., continued to show a slight decrease in the Cr^{51} half-life of 23 days. Despite evidence of a normal red cell life span, these patients had a progressive decline in hematocrit values over a 2- to 3-month period (Table 1). Thus, they apparently had inadequate erythroid tissue remaining to maintain normal red cell values. However, the elimination of severe hemolysis by splenectomy was associated with a welcome reduction of the need for transfusions. Weinstein and Le Roy[12] have reported one patient with myeloid metaplasia with a Cr^{51} red cell half-life of 18 days as studied with genotype specific tagged red cells. From the present study one may conclude that the patient's own red cells would show a similar increased rate of destruction.

Previous studies have indicated that the Ashby survival time of normal donor cells in recipients with thalassemia minor may be normal (100 to 120 days). However, red cells from patients with thalassemia minor may apparently have either a normal or shortened Ashby survival in normal recipients[6]. One patient with thalassemia minor was studied before and after splenectomy. A moderately increased hemolysis was observed before splenectomy with a Cr^{51} half-life for the red cells of 15 days. After splenectomy a normal survival of red cells was observed with a half-life of 25 days. The decreased Cr^{51} survival of red cells in this patient was attributed to increased red cell destruction associateded with splenomegaly. Previous publications have emphasized the hemolytic component to this disease that may exist with marked splenomegaly[13].

In the patient with lymphatic leukemia, one may note good agreement between the 2 curves of red cell destruction during the short period of observation. Ashby counting was difficult to evaluate in this patient because of nonspecific clumping of the red cells.

Repeated observations were necessary to obtain red cell suspensions without this artefact. The presence of abnormal agglutinins and other protein factors often makes Ashby counting difficult in acquired hemolytic disease. The Cr^{51} method avoids this problem. Another patient with a long history of idiopathic acquired hemolytic anemia (W. O.) was studied to evaluate the effect of cortisone acetate on hemolysis. Although the half-life period was prolonged from 7 to 10 days during the administration of 200 mg. per day of cortisone acetate orally, the patient could not be observed over a long enough period to determine the significance of this slight change. Weinstein and Le Roy[12] have reported similar results in patients with acquired hemolytic anemia. They also demonstrated the value of the Cr^{51} method for observing changes in the survival of the red cell while the patient is receiving specific treatment.

The Cr^{51} technique requires venous blood for estimation of red cell radioactivity; while Ashby studies may be done with capillary samples if necessary. The limitation of sample size associated with the radioactivity hazard indicates that tagging of red cells by this method is inadvisable in infants and small children.

In contrast to these limitations the Cr^{51} method has many advantages. Utilizing the technique outlined, red cells may be tagged easily with a minimal amount of trauma. The red cells are not washed with saline and one may expect them to be representative of the normal population. In severe hemolytic disease, washing of red cells may result in longer survival periods than expected if the more fragile red cells are selectively hemolyzed; alternatively, a steep initial slope may be due to damage in preparation of the cells. The use of a closed plastic bag system also lessens the opportunity for contamination which is always present when red cells are washed repeatedly. Its disposability reduces the hazards of radioactive contamination and the problems of decontamination. The Cr^{51} technique has advantages over the Ashby method in that preliminary phlebotomy is unnecessary as small quantities of blood can be used. It also avoids the hazards of blood group sensitization and serum jaundice. This technique is not limited in its application by the presence of suitable blood groups and is able to evaluate the turnover of the patient's own cells in his body. As with other radioactive methods its statistical reproducibility is much greater than techniques which depend upon agglutination and other biological phenomena.

Summary. 1. Small samples of blood from both normal and anemic individuals have been tagged with radioactive chromium, using a technique which avoids damaging the red cells.

2. The survival of the tagged cells after re-injection has been followed and compared in some cases with simultaneous Ashby studies.

3. The results show that in healthy individuals, cells tagged with chromium have a normal life span. The radioactivity leaves the circulation in an exponential fashion which is reproducible in healthy men.

4. In the various hemolytic and hypoplastic disorders studied, the manner of removal of the tagged cells from the circulation was in essential agreement with other hematological data and did not appear to be significantly affected by the labelling process itself.

5. These results have been discussed and the advantages and disadvantages of this technique for the study of blood disorders compared with the classical Ashby method.

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THE ASSOCIATION OF CORONARY OCCLUSION AND INFARCTION WITH DIABETES MELLITUS A NECROPSY STUDY*

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The frequency of the association of cardiovascular disease with diabetes mellitus has been commonly noted. In diabetes, there is a disturbance not only of sugar metabolism, but also of that of fat. It has long been known that the blood in diabetes contains an excess of lipid substances. It is beyond the scope of this paper to elaborate on the complex problems of cholesterol and lipid metabolism. According to Duncan[1], the most common and striking abnormalities associated with fat metabolism in untreated diabetics are: (1) excess cholesterol in the circulation, (2) increased blood fats, and (3) an accumulation of ketone bodies in the blood. It is generally accepted that there is a greater prevalence of atherosclerosis and clinical coronary disease associated with diabetes. Nathanson[7] and many others have emphasized that the essential cardiac lesion in diabetes is coronary sclerosis. Petersen[8] observed that the blood phospholipids and cholesterol averaged higher in the diabetic than in the normal group. Similarly, according to Steiner and Domansky[11], and Gertler *et al.*[4], and others, lipid values are also often elevated in coronary heart disease. Accordingly, one should find a greater number of cases of coronary heart disease associated with diabetes.

In a study of 1,319 consecutive adult necropsies, we found 137 cases of diabetes mellitus, an incidence of 10.4%. Of these, 60 revealed evidence of coronary occlusion and infarctions, an incidence of 43.8%. The latter incidence seemed to be very high, but this could be accounted for by the large number of Jewish admissions to the hospital. In this group one would expect to find a greater number of diabetics since this disease is more prevalent among this race. A study was made of the above cases with a comparison of the data already recorded in the literature, in order to determine whether or not this is the true incidence of coronary disease associated with diabetes mellitus. In a review of the literature it was found that the necropsy incidence of coronary disease associated with diabetes varied from 28 to 52.3%. In our 137 cases of adult necropsies with diabetes mellitus, we found 60 or 43.8% of the cases with coronary heart disease. Among 60 cases, there were 6 instances of coronary occlusion without infarction and 54 with coronary occlusion and infarction. Root *et al.*[9] in 349 diabetic necropsies found 112 cases with coronary occlusion, an incidence of 32.0%. Enklewitz[2], in 92 diabetic necropsies found an incidence of 28.2%.

*We are indebted to Dr. Tobias Weinberg, Head of the Department of Laboratories, for the privilege of using the necropsy material in this study.

In a clinical study of coronary disease associated with diabetes, Hepburn and Graham[5] in 123 cases of diabetes found evidence of electrocardiographic changes indicative of coronary heart disease in 45.5%. In 150 clinical cases of diabetes reported by Enklewitz[2], and Stearns *et al.*[10], 34% were found to have coronary heart disease.

The incidence of coronary occlusion and infarctions among diabetics was then compared with the incidence in our total number of necropsies. In 1,182 adult nondiabetic necropsies the incidence of coronary heart disease was 20.1% while the incidence among our diabetic necropsies was 43.8%. Table 1 shows the comparative incidence of coronary heart disease with and without diabetes.

TABLE 1.—COMPARATIVE INCIDENCE OF CORONARY HEART DISEASE WITH AND WITHOUT DIABETES

	Coronary occlusion and infarction in the diabetic %	*Coronary occlusion and infarction in the nondiabetic* %
Root *et al.*[9]	32.0	6.0
Stearns *et al.*[10]	34.0	14.0
The Authors	43.8	20.1

In a review of the adult necropsy records, especially in the older age group, the most striking feature is the prevalence of vascular changes. In almost all necropsies in adults some degree of cardiovascular abnormality can be seen. When a comparative study is made of necropsy material, it is difficult to compare these findings, since in both the diabetic and nondiabetic, similar changes occur. However, one obtains the impression that the degree of cardiovascular changes is greater in the diabetic patient.

In addition to the coexisting coronary occlusion and infarctions in our 60 diabetics, there were other cardiovascular changes noted in our 137 cases of diabetes mellitus. Table 2 shows the various vascular findings in these cases.

TABLE 2.—CARDIOVASCULAR ABNORMALITIES IN 137 CASES OF DIABETES MELLITUS

	Cases
Coronary occlusion and infarctions	60
Coronary atherosclerosis	125
Coronary vessel narrowing	95
Myocardial fibrosis	81
Dilatation and hypertrophy of ventricles	93
Calcification of mitral or aortic valves or both	26
Pulmonary and aortic arteriosclerosis (grossly significant)	104

In this necropsy study the coronary lesions included not only the acute lesions contributing to death, but in many instances there were old healed lesions of coronary occlusion or infarctions, or both. It must also be pointed out that many of the above cardiovascular changes were observed with and without the presence of an occlusion and infarction.

It was of interest to note the condition of the cardiac valves and the coronary arteries in the diabetic and nondiabetic patient. Lundbaek and Petersen[6] made chemical studies of the coronary arteries in the diabetic and nondiabetic patients and found that the calcium content was lower in the arteries from the diabetic. In our 137 cases of diabetes, there were 26 instances with calcification of the mitral or aortic valves, or both, an incidence of 19%. In a recent study of 165 cases of cholesterosis of the gallbladder, there were 20 instances of calcification of the valves, an incidence of 12%. Although the cases are too few to evaluate the incidence of valvular calcification in the diabetic, this difference may be significant. Lundbaek and Petersen[6] further observed that the cholesterol and phospholipid content of the arteries show no significant difference

in the diabetic and nondiabetic, but the proportion of the phospholipid constituents was different in the two groups, the cephalin content being higher and the lecithin content probably lower in the arteries from the diabetic patients than in those from nondiabetic patients.

TABLE 3.—AGE DISTRIBUTION OF DIABETICS WITH AND WITHOUT CORONARY HEART DISEASE

Age group	*Diabetes associated with Coronary Heart Disease Cases*	*Diabetes without Coronary Heart Disease Cases*
20-30	0	2
30-40	0	1
40-50	6	10
50-60	15	16
60-70	22	28
70-80	14	15
80-90	3	5
Total number of cases	60	77

groups of cases, there appears to be little age difference between the diabetics with coronary occlusion and those without occlusion. It is important to mention that the ages given are not the age at the time of the occlusion and infarction, but the age of the patient at death. Since many of the coronary lesions were of long standing, one must assume that the onset of the coronary heart disease occurred at a younger age.

It is of interest to note the sex ratio in this study. Among the total of 137 diabetic cases, there were 39.4% males and 60.6% females. Of the 60 diabetics with coronary occlusion, 40% were males and 60% females, and in the 77 diabetics without coronary occlusion, the sex incidence was comparable. The higher incidence of diabetes mellitus among females is in accord with other statistical studies. On the other hand, statistics in the adult population generally show that

TABLE 4.—THE SEX INCIDENCE IN DIABETES MELLITUS WITH AND WITHOUT CORONARY DISEASE

	Diabetes Mellitus		*Diabetes Associated With Coronary Occlusion*		*Diabetes Without Coronary Occlusion*	
	Cases	*%*		*%*		*%*
Males	54	39.4	24	40.0	30	39.0
Females	83	60.6	36	60.0	47	61.0
Total cases	137		60		77	

The age of the patient is presumed to be a significant factor in the development of cardiovascular disease in diabetic patients. It is well known that vascular changes generally develop at an earlier age in the diabetic. The age distribution of the diabetics with coronary occlusion and infarction in our series is compared with that of the cases without coronary disease (Table 3). The coronary lesions occurred predominantly in the 6th and 7th decades.

On comparing the ages in the two

males predominate among patients with coronary occlusion and infarctions, in contrast to the predominance of females in our group. Duncan[1] has likewise noted that there is an increased incidence of disease of the coronary arteries in diabetic women. The data relative to sex are shown in Table 4.

Summary. In 1,319 consecutive adult necropsies, we found 137 cases of diabetes mellitus, an incidence of 10.4%. Among these, there were 60 cases asso-

ciated with coronary occlusion and infarctions, an incidence of 43.8%. The incidence of the association of coronary heart disease in diabetics, (43.8%) was compared with 20.1% incidence of coronary occlusion and infarctions noted in our study of the necropsy findings in nondiabetic adults. This indicates that coronary occlusion is twice as prevalent in the diabetic as in the nondiabetic. Previous observers are generally agreed that the degree of cardiovascular change is greater in diabetic than in nondiabetic patients, and that its onset occurs at an earlier age. In our series the sex ratio was the same in the diabetic group with, as in that without, associated coronary occlusion. In both groups there was a decided preponderance of females (60 and 61% respectively). This is in contrast to the predominance of males among patients with coronary disease but without diabetes.

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CARDIAC ENLARGEMENT FOLLOWING MITRAL COMMISSUROTOMY

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Cardiac enlargement is anatomic evidence of an undesirable load imposed upon the heart. Palmer[4], in his classic paper on the development of cardiac enlargement, states that cardiac enlargement and cardiac failure are different stages of the same process. Taussig and Goldenberg[7], likewise, used a radiologic method in their, also classic, study on the prognosis of rheumatic heart disease. Grant[2] came to the same conclusion in studies on prognosis in the adult. More recently, White and his associates[9] re-emphasized the prognostic importance of cardiac size.

There is no doubt that cardiac enlargement is an index of the degree to which the heart calls upon its reserve. The larger the heart, other things being equal, the worse is the prognosis. This statement is particularly true when applied to a single type of heart disease and is most applicable when changes in heart size in a single individual are observed. Indeed, the rate at which increase in size occurs and the circumstances which determine it are important guides both to prognosis and to treatment.

Mitral commissurotomy is based upon the concept of, at least partial, passive distention of those portions of the heart proximal to the obstruction. One would think, therefore, that mitral commissurotomy, if successful, would, at least partly, deflate these proximal chambers and that radiologic studies, similar to those of Palmer and Taussig, would demonstrate a decrease in size of these chambers, as a corollary to the diminution of the obstruction. To our surprise, not only did we fail to observe a decrease in size, but we actually observed, in most cases, an increase in size, not only of chambers proximal to the obstruction but, also of other portions of the heart.

Our purpose is to report these roentgenologic findings and to discuss their significance.

Material and Method. Serial roentgenologic studies were made of 44 consecutive individuals subjected to mitral commissurotomy. Of these 44, 7 died and 17 could not be followed roentgenologically for a minimal postoperative interval of 6 months because of geographic or other reasons. All of these had, at their last study, a cardiac silhouette larger in size than that present before operation but they have not been included in the present analysis for reasons to be given later.

Of the remaining 20, all had serial roentgenograms for at least 6 months after operation and some for as long as 2 years. Each had a minimum of 5 separate studies. There were 16 females and 4 males, from 5 to 57 years of age.

Roentgenologic study of cardiac size, to be accurate, must avoid two potential fallacies. One is failure to use, as a control, a roentgenologic study after maximal compensation, prior to surgery, has been obtained. The other fallacy involves roentgenologic technique. Roentgenograms, to be comparable, must have a constant target-film distance, a constant centering of patient and film, identical position of the leaves of the diaphragm and superimposable bony landmarks. Every effort was made to satisfy these requirements which, at times, was difficult (for example, pain) or impossible (for example, paralysis of the left leaf of the diaphragm). Tracings of films taken in the anterior, lateral and both oblique projections were made on transparent paper to facilitate comparisons and to justify conclusions. This method is important to avoid illusions created, at times, by surgical amputation of the left auricular appendage. In case of doubt, we preferred to call the postoperative cardiac silhouette unchanged or smaller. Silhouettes reported as larger are unquestionably so.

Results. Immediately following operation, the so-called cardiac silhouette enlarges moderately to massively in all instances. This enlargement is universal and appears to involve all chambers of the heart. Indeed, at this time, the individual chambers of the heart cannot be clearly delimited, because the junctions of the chambers are not clearly defined. The cardiac silhouette was at its maximum size and much larger than the silhouette present preoperatively in all individuals who died. It was also larger than that present before operation in all individuals who could not be followed roentgenologically for a period of at least 6 months.

Of the 20, who form the basis of this report, one showed a rapid increase in size of the cardiac silhouette until the third week after operation, when, because of signs suggestive of cardiac tamponade, two pericardiocenteses were done and yielded a total of 210 cc. of serosanguineous fluid. In the others, after initial rapid enlargement, the cardiac silhouette remained stationary in size, usually for 2 to 6 weeks. The silhouette gradually diminished and usually reached its minimal size in 3 months. Rarely, further gradual decrease occurred for another 3 months. It is for this reason and, also, to exclude, as far as possible, any pericardial reaction due to surgery that we chose 6 months as the time of the maximal beneficial results of mitral commissurotomy from a roentgenologic viewpoint.

The results are given in Table 1. Four of the 20 patients had no change in over-all size of the cardiac silhouette. This is illustrated in the roentgenograms of the following patient:

CASE 1. L.M., a 43-year-old woman with rheumatic heart disease, mitral stenosis and sinus rhythm had a mitral commissurotomy on May 14, 1953. Upon hearing of her son's induction into the army, she suddenly developed cough and hemoptysis 2 weeks before operation. Another son is overseas with the army. She had had bouts of fever and polyarthritis between the ages of 8 and 12 years but never had any prolonged period of bed rest. Mitral stenosis was discovered at a routine examination during her sixth pregnancy, 12 years ago. She has 7 children, 9 to 23 years old. Pregnancies were uneventful. She has taken digitalis every day for 12 years because of shortness of breath on effort and intermittent ankle swelling. Three years ago, ankle edema became persistent. Since then, mercurial diuretics have been necessary once every 2 to 3 weeks. She denied any chronic cough or previous hemoptysis.

Examination of the heart revealed a slightly palpable apical impulse that was located in the 5th intercostal space at the left mid-clavicular line. The rhythm was regular at 80 per minute. M_1 and P_2 were accentuated. A presystolic rumbling murmur was audible at the apex. The lungs were clear. The veins were not distended. The liver and spleen were not palpable. There was no edema. The blood pressure was 120/80 mm. Hg. The venous pressure was 12 centimeters (fluid), the ether time 4 seconds and the decholin time 12 seconds.

Chest roentgenogram (Fig. 1A) disclosed no cardiac enlargement. The left upper border was straight. The esophagus, in the region of the left atrium, was minimally displaced dorsad and to the right. Electrocardiogram re-

TABLE 1.—COMPARISON OF THE CARDIAC SILHOUETTE AND PULMONARY MARKINGS AT LEAST 6 MONTHS FOLLOWING MITRAL COMMISSUROTOMY WITH THE LAST PREOPERATIVE STUDY

Over-all Size	*Subject*	*Left Second Segment*	*Left Third Segment*	*Hilar and Pulmonary Markings*	*Right Ventricle*	*Left Atrium*
Smaller (5)	G. D.	−	0	−	0	0
	M. C.	0	−	−	0	0
	S. W.	0	−	−	0	0
	R. L.	−	−	−	0	0
	S. N.	0	0	−	0	0
Unchanged (4)	L. M.	0	−	0	0	0
	R. W.	−	−	0	0	0
	D. W.	0	−	−	0	0
	M. E.	0	−	0	+	0
Larger (11)	A. F.	+	0	+	+	+
	E. P.	+	+	0	+	0
	M. H.	+	0	+	+	+
	F. D.	0	−	0	+	0
	M. S.	0	+	+	+	+
	M. W.	0	−	0	+	0
	I. D.	0	−	0	+	0
	M. T.	0	−	0	+	0
	E. H.	0	−	0	+	0
	E. J.	0	−	0	+	0
	F. K.	0	−	0	+	0

Key: + = Increase; 0 = Unchanged; − = Decrease.

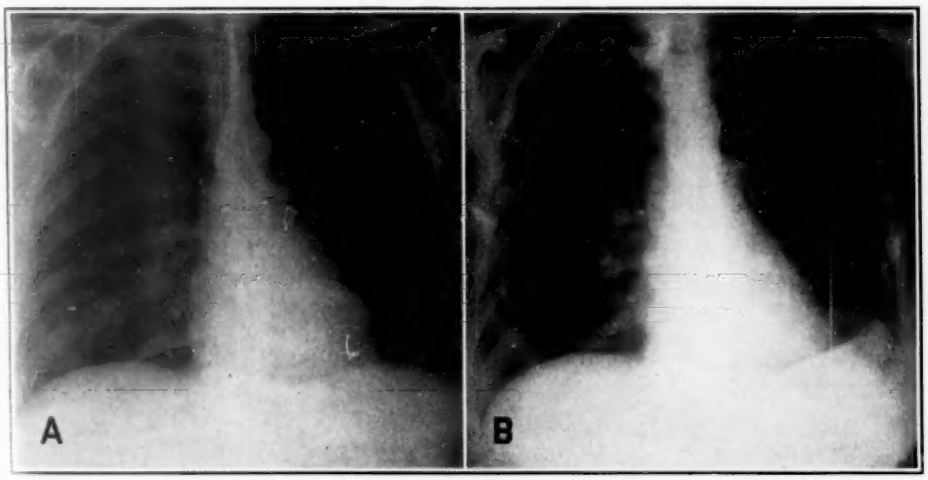

Fig. 1.—Chest roentgenograms, anterior projection, taken on May 11, 1953, (A), and August 10, 1953, (B). Case 1, L.M., Operative date, May 14, 1953. The preoperative chest roentgenogram shows a cardiac silhouette that is not increased in size. The left border is straight. Chest roentgenogram 6 months after operation is similar to the one taken in August, 1953, that shows a cardiac silhouette that is unchanged in over-all size but with less prominence of the left third segment and, in addition, a left pleural reaction. The chest roentgenograms in the oblique projection also revealed an unchanged over-all size of the cardiac silhouette.

vealed slightly broadened and notched P waves.

At operation, the mitral orifice was centrally located and admitted the tip of the finger. Following incision of the anterolateral commissure, the mitral orifice admitted 1½ fingers. A slight degree of regurgitation was present before and after operation. Biopsy of the left auricular appendage revealed swollen, pale muscle fibers and distorted nuclei but no Aschoff cells.

Following operation, she developed chest pain and dyspnea. The alae nasi dilated with inspiration and the respiratory rate was increased. A pericardial friction rub was audible from May 16 to May 18, 1953. The electrocardiogram disclosed characteristic signs of pericarditis. The chest roentgenogram showed slight enlargement of the cardiac silhouette. An apical systolic murmur (grade 2) appeared after operation. A blowing diastolic murmur appeared on May 22, in the left parasternal region, and was of maximal intensity at the level of the third intercostal space. The ankles were slightly edematous. Mercurials were administered and digitalis continued. Otherwise, convalescence was uneventful and the patient was discharged on May 23, 1953. Two days later, she was readmitted because of severe pain, substernally and in the left anterior chest, which was accompanied by fever and profuse perspiration. Examination of the heart revealed the parasternal diastolic murmur and apical systolic and presystolic murmurs. Salicylates were given and the fever and pain gradually subsided. She was discharged in 10 days. Digitalis was continued in the same dose as taken before operation. Mercurial diuretics were given occasionally with resultant diuresis and weight loss. She continued at bed rest, at home, until August, 1953, when she resumed some of her household chores. Meanwhile, fever and pain were experienced intermittently and ankle edema became persistent. Her physician gave her a mercurial diuretic once a week, although edema did not completely disappear after an injection. Cough and dyspnea on effort appeared in August and have been present since.

In February, 1954, her temperature rose to 100° on three occasions during a period of 2 weeks. She continues to sweat frequently, particularly at night.

She continues doing her housework, although she has shortness of breath on effort and ankle edema. Salicylates (0.6 gm. q.i.d.) are taken every day. Examination discloses jugular venous distention and pitting edema of the legs and feet. The apex impulse is lifting in character but not displaced. The parasternal diastolic, and apical systolic and presystolic murmurs remain. The rate is 80 per minute and regular. The blood pressure is 120/70 mm. mercury. Chest roentgenogram is similar to that taken in August, 1953, (Fig. 1B) that shows the over-all size of the cardiac silhouette unchanged compared to the preoperative study. Electrocardiogram is similar to that obtained before operation.

Five of the 20 patients had a minimal over-all decrease in size of the cardiac silhouette. The sequence of cardiac enlargement after mitral commissurotomy followed by gradual decrease to a size slightly smaller than that existing before operation is illustrated in the roentgenograms of the following patient who was reported in detail elsewhere[6]:

CASE 2. S.N., a 36-year-old woman with rheumatic heart disease, mitral stenosis and sinus rhythm, had a mitral commissurotomy on May 15, 1952. The mitral orifice was markedly contracted and, following several incisions of the anterolateral commissure, admitted 1½ fingers. No regurgitant jet was present before or after operation. Biopsy of the left auricular appendage showed endocardial thickening and cellular infiltration but no Aschoff cells. Postoperatively, a pericardial friction rub was audible from May 16 to May 20, 1952. Later, she developed recurrent bouts of chest pain, arthritis, fever and heart failure. In July, 1952, atrial fibrillation occurred and was converted to sinus rhythm by quinidine. At present, more than one and a half years after operation, she is increasingly dyspneic and continues to experience bouts of chest pain, fever and arthralgia. Chest roentgenograms are shown in Fig. 2.

Eleven of the 20 patients had an over-all larger cardiac silhouette. This is illustrated in the roentgenograms of the following patient:

CASE 3. E.P., a 30-year-old woman with rheumatic heart disease, mitral stenosis and sinus rhythm, had a mitral commissurotomy on June 19, 1952. She had polyarthritis during childhood but first became aware of heart disease during the fifth month of pregnancy, in 1949, when she had shortness of breath and ankle edema. During the seventh month, when she went into labor, she de-

veloped acute left ventricular failure with pulmonary edema. She was delivered of twins. One was stillborn and the other died in a few days. Following pregnancy, fever and migratory polyarthritis appeared and remained for 2 months. She gradually recovered and felt well until 1950, when, following a respiratory infection, she developed hemoptysis and heart failure. She was again placed on a cardiac regimen with benefit. In 1951, another respiratory infection precipitated heart failure. Following this episode,

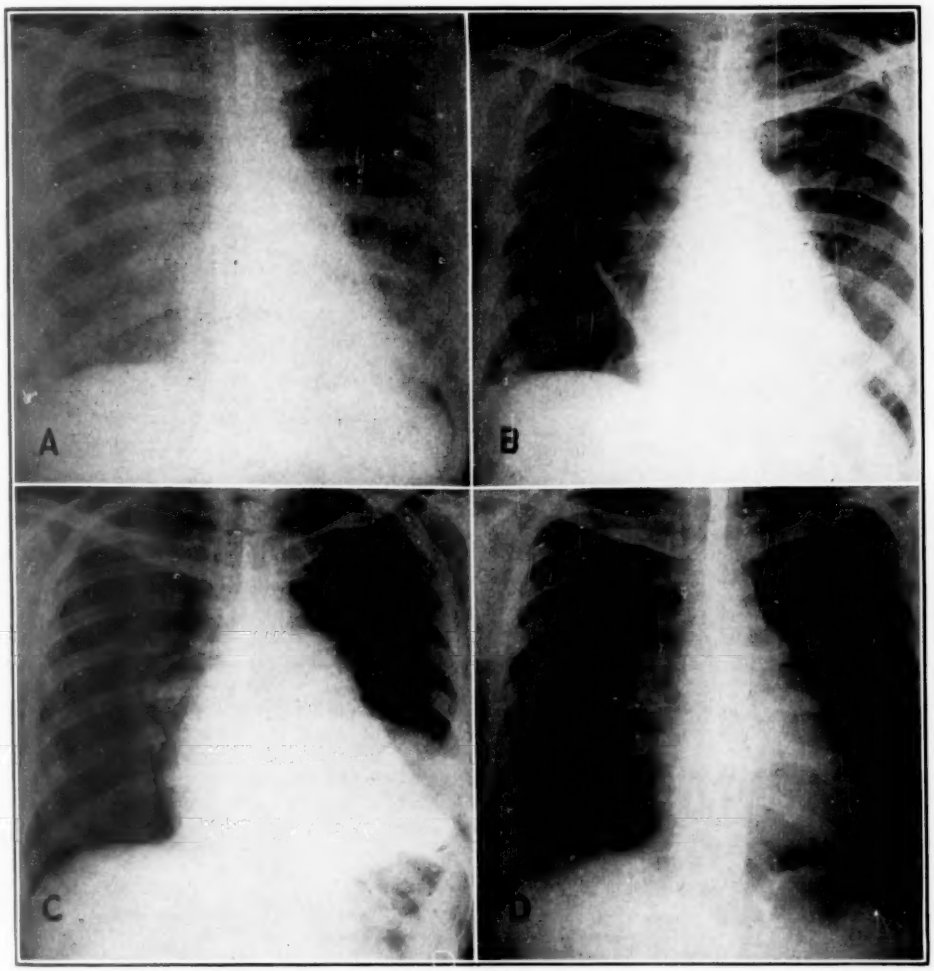

Fig. 2.—Chest roentgenograms, anterior projection, taken on May 9, 1952, (A), May 27, 1952, (B), July 7, 1952, (C), and September 25, 1953, (D). Case 2, S.N., operative date, May 15, 1952. The preoperative roentgenogram reveals pulmonary congestion and a cardiac silhouette that is slightly enlarged with straightening of the left upper border. Following operation, there is marked enlargement of the cardiac silhouette. Note the marked outward convexity of the pulmonary segment in the chest roentgenogram taken on July 7, 1952 (C). The chest roentgenogram taken one and one-half years after operation, (D), shows that the size of the cardiac silhouette is slightly smaller than existed before operation. There is less pulmonary congestion.

she had marked fatigue and required frequent mercurial diuretics because of ankle edema.

Examination preceding operation disclosed no cardiac enlargement. A presystolic apical murmur was audible. There was no evidence of heart failure. Chest roentgenogram (Fig. 3A) showed a slightly enlarged heart with bulging of the left second segment and enlargement of the left atrium and right ventricle. Electrocardiogram revealed broad and notched P waves.

On the advice of her physician, Dr. Leroy L. Walker, Jr., she has taken salicylates continuously since operation. She feels much better and even scrubs floors without experiencing dyspnea. In April, 1953, she stopped salicylates of her own accord and developed pain in the right chest with fever that disappeared quickly when salicylates were resumed. Examination, at present, discloses an apical systolic murmur (grade 2), a mid-diastolic rumble and sinus rhythm. Chest roentgenogram (Fig. 3B) reveals increase in heart size. She remains on digitalis but has not taken any mercurial diuretic since operation.

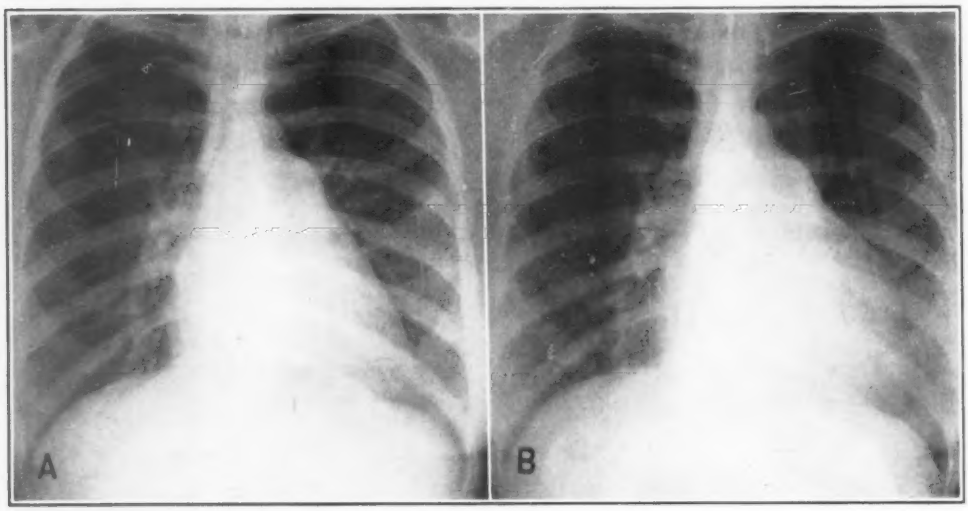

Fig. 3.—Chest roentgenograms, anterior projection, taken on June 17, 1952, (A) and July 2, 1953 (B). Case 3, E.P., operative date, June 19, 1952. The preoperative roentgenogram, (A) shows enlargement of the cardiac silhouette with bulging of the left second segment and a double contour on the right lower border. The roentgenogram taken more than one year after operation, (B), shows a marked increase in the size of the cardiac silhouette. There is bulging of the left second segment, increased prominence of the left third segment and increased curvature of convexity of the left lower border. The pulmonary vascular markings are unchanged.

At operation, the mitral orifice was said to be of the size of 3 matchstick heads. The leaflets were thickened but pliable. After incision of the anterolateral commissure, the mitral orifice admitted 2 fingers. A slight degree of regurgitation appeared after surgery. Biopsy of the left auricular appendage revealed Aschoff bodies.

A pericardial friction rub was audible from June 20 to July 1, 1952. The electrocardiogram revealed upward displacement of J and flattening of the T wave. Convalescence was, otherwise, uneventful and she was discharged on July 1, 1952.

Enlargement of the cardiac silhouette long after mitral commissurotomy is also illustrated in the roentgenograms of the following patient who was described in detail elsewhere[6].

CASE 4. A.F., a 40-year-old woman with rheumatic heart disease, mitral stenosis and atrial fibrillation, had a mitral commissuro-

tomy on October 23, 1952. The mitral orifice was of the size of 2 matchstick heads. Extensive calcification was present. Following incision of the anterolateral and posteromedial commissures, the orifice admitted 1½ to 2 fingers. No regurgitant jet was felt either before or after operation. Three weeks later, chest pain, fever and heart failure occurred. Since

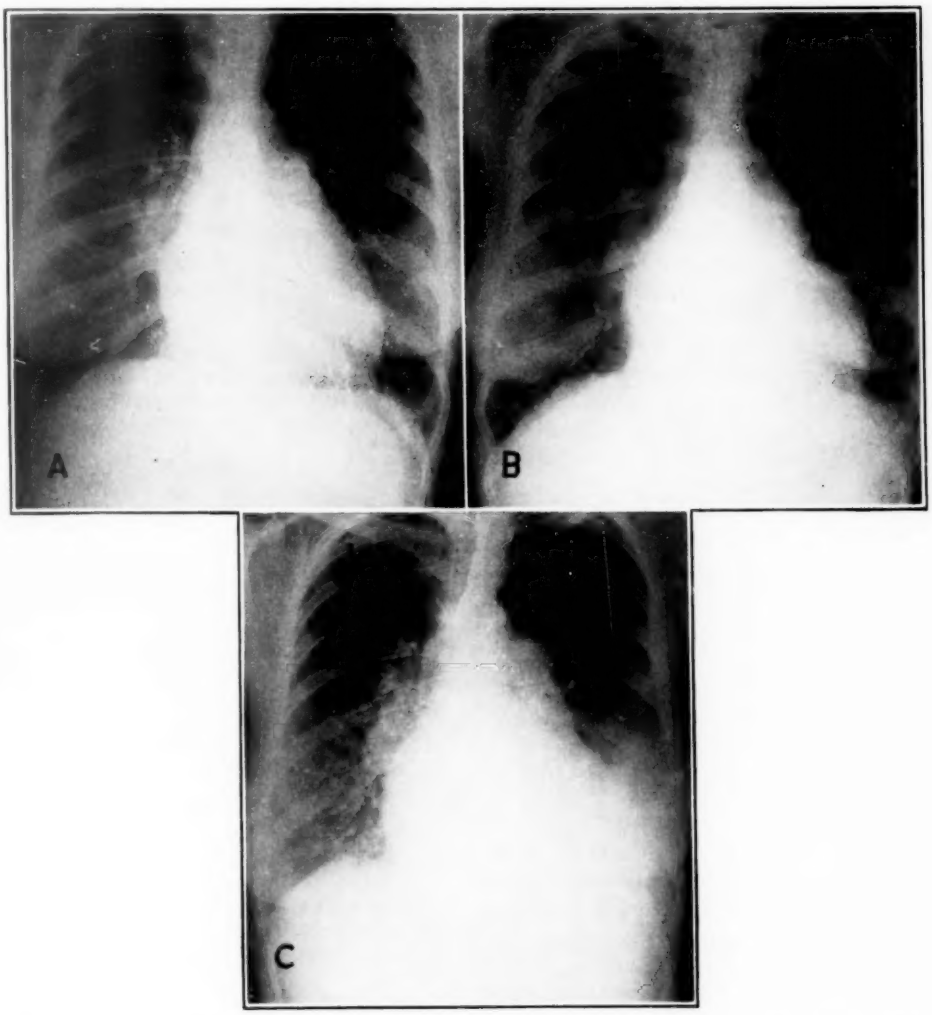

Fig. 4.—Chest roentgenograms, anterior projection, taken on October 15, 1952, (A), July 3, 1953, (B), and February 22, 1954, (C). Case 4, A.F., operative date, October 23, 1952. The preoperative roentgenogram, (A), reveals enlargement of the cardiac silhouette with straightening of the left border, enlargement of the left atrium and outflow tract of the right ventricle. The roentgenogram taken 9 months after commissurotomy, (B), shows a larger cardiac silhouette with concavity of the left third segment and rounding of the left ventricular border. The left atrium, as seen on the right border, is larger. Sixteen months after commissurotomy, the roentgenogram, (C), shows marked bulging of the left upper border, very prominent pulmonary vascular markings and a left pleural effusion.

that time, there have been frequent recurrences. At present, there is an apical systolic murmur in addition to the murmur of mitral stenosis. The liver is markedly enlarged and tender. The jugular veins are distended. Pitting edema of the legs and feet is present. A mercurial diuretic is needed at least once a week. Chest roentgenograms are shown in Fig. 4.

The most striking change in the cardiac silhouette, as seen in the anterior projection, is the decrease or absence of the left third segment, presumably due to surgical amputation of the left auricular appendage. This absence produces, at times, an illusion of a smaller cardiac silhouette. Careful observation, aided, if necessary, by superimposed tracings on transparent paper, proves the illusory nature of the smaller size of the cardiac silhouette. Actually, the left ventricular segment appears, under such circumstances, more rounded. However, in the left anterior oblique projection, the posterior border is not as rounded, as is commonly seen with excessive enlargement of the left ventricle, but, is rather obliquely linear with inferior angulation. More striking is the enlargement of the right ventricle, as judged, in the same projection, by its increased curvature of convexity and its encroachment upon the anterior free space.

In no instance, where we have been able to delineate the left atrium, either within the cardiac density or on the right border in the anterior projection or by its displacement of the barium-filled esophagus, have we noted any decrease in its size. On the contrary, in 3 instances, definite increased dorsad displacement of the barium-filled esophagus was noted. Indeed, in 2, we observed, in the anterior projection, increased prominence of the left third segment.

Discussion. The changes in cardiac size, whether in the direction of increase or decrease, were, in most instances the result of over-all generalized changes and not the result primarily of changes in those portions of the heart proximal to the obstruction of mitral stenosis. The only exception to this statement is the decrease or absence of the left third segment presumably due to surgical amputation of the left auricular appendage.

The decrease in the over-all size of the heart was minimal. Of the 5, one, by error, had his last preoperative roentgenologic study 3 weeks before operation. The chest roentgenograms of this patient, Case 5, are shown in Fig. 5.

CASE 5. G.D., a 49-year-old man with rheumatic heart disease, mitral stenosis and atrial fibrillation, had a mitral commissurotomy on June 16, 1953. Pulmonary infarction, manifested by cough, chest pain and hemoptysis, occurred on May 12, 1953, and precipitated heart failure, for which he was admitted to the hospital. He had chorea, at the age of 10 years but was first aware of heart disease in 1952 when he had palpitations, shortness of breath and fatigue. He was given digitalis. Symptoms recurred at monthly intervals. He stopped working in January, 1953. Mercurial diuretics were administered weekly. In May, 1953, he developed acute dyspnea with chest pain and hemoptysis followed by the appearance of ankle edema.

Examination disclosed the apical impulse to be in the sixth intercostal space at the left mid-clavicular line. A systolic murmur (grade 2) and a diastolic rumble were present at the apex. The rhythm was irregular at a ventricular rate of 100 per minute. M_1 and P_2 were accentuated. Basilar rales were present bilaterally. The liver was slightly enlarged and tender. Pitting edema of the ankles was present. The blood pressure was 110/80 mm. Hg.

Chest roentgenogram (Fig. 5A) disclosed enlargement of the heart with prominence of the left atrium and right ventricle, and pulmonary congestion. Linear infiltrates were present in the right lower lobe. Electrocardiogram showed atrial fibrillation. Following compensation, operation was performed. The mitral orifice was slit-like and extensively calcified. Following incision of the anterolateral commissure, the orifice was said to be 22 by 22 millimeters. A slight degree of regurgitation was present before and after sur-

gery. Biopsy of the left auricular appendage revealed no Aschoff cells.

Following surgery, he received cortisone. Other than severe chest pain, convalescence was uneventful and he was discharged on June 29, 12 days after operation. The cardiac findings were unchanged. There was no evidence of failure. He felt very much better. Digitalis was continued. Chest roentgenogram (Fig. 5B) taken almost 2 months after operation revealed a decrease in the size of the cardiac silhouette and less prominence of the pulmonary vascular markings. The density in the right lower lobe disappeared.

In February, 1954, he developed a cough productive of yellow expectorate. Shortness

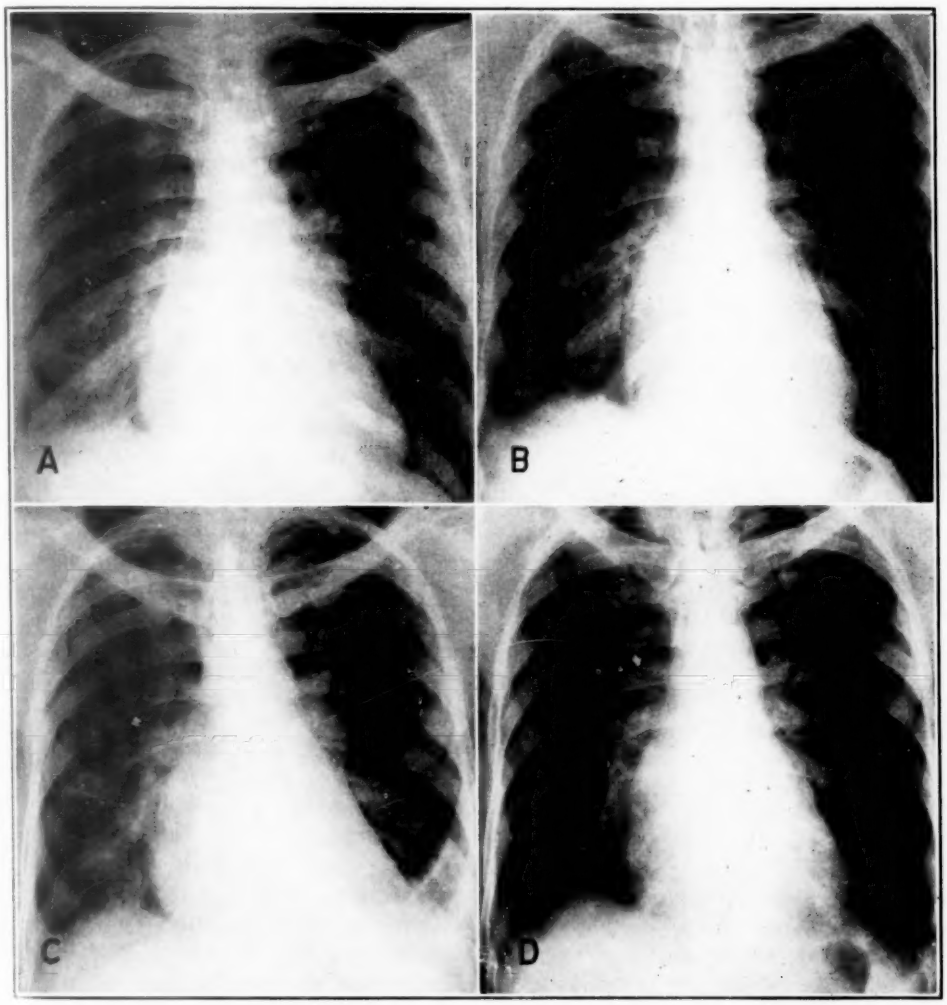

Fig. 5.—Chest roentgenograms, anterior projection, taken on May 18, 1953, (A), August 6, 1953, (B), February 19, 1954, (C), and February 23, 1954, (D). Case 5, G.D., operative date, June 16, 1953. In (A), note the density in the right lower lobe which represents a pulmonary infarction that precipitated heart failure. Following surgery, heart size decreased (B). In (C), the size of the cardiac silhouette is as large as it was before operation. Four days later, chest roentgenogram, (D), shows marked decrease in over-all size of the cardiac silhouette and disappearance of signs of congestion.

of breath appeared and was progressive. The ankles became edematous. He was readmitted to the hospital. Rectal temperature was slightly elevated. Atrial fibrillation was present with a ventricular rate of 120 per minute. A systolic (grade 3) murmur and diastolic rumble were audible at the apex. The jugular veins were distended, and bilateral pleural effusion, tender and enlarged liver and ankle edema were present. Chest roentgenogram (Fig. 5C) showed a marked increase in size of the cardiac silhouette. Digitalis was increased and penicillin was given. In a few days, the patient was tremendously improved. The signs of failure disappeared. Chest roentgenogram (Fig. 5D), 4 days after admission, showed a marked decrease in size of the cardiac silhouette. He was discharged on a maintenance dose of digitalis and weighed 10 pounds less than when he was admitted.

The second patient who showed a minimal decrease in over-all size of the heart also had a pulmonary infarction 2 weeks before operation. A third patient had recurrent bouts of infection of the respiratory tract. The fourth patient had been completely compensated and required no digitalis until 3 months before operation, when she began to cough and experience ankle edema and orthopnea. The last patient had been and still is under the care of a psychiatrist for obscure emotional problems. The minimal and generalized nature of the decrease in cardiac size is not unlike that seen following compensation after a successful medical regimen (Figs. 5C and 5D).

On the other hand, the findings 6 months after mitral commissurotomy of an over-all enlargement of the cardiac silhouette in 55% of 20 patients, of apparent enlargement of the right ventricle in 60%, of at least no decrease in size of the left second segment in 85% and no decrease in size of the left atrium (except that due to surgical amputation) in all instances, and actually an increase in some, are all indications, that, if enlargement of structures proximal to mitral stenosis are due, in part, to passive distention because of obstruction, the surgeon has failed to relieve the obstruction. Indeed, from the roentgenologic viewpoint, these individuals would be regarded as worse than they were before operation.

Cardiologists have recognized for a long time that cardiac enlargement has prognostic significance. The heart does not enlarge unless there is some pathophysiologic disturbance. In rheumatic heart disease, progressive cardiac enlargement has long been considered a sign of active carditis. It is not the constant load but the increased amount of work and increased strain which cause the enlargement. In children, Taussig[7] showed that in coarctation of the aorta with extreme hypertension, the heart does not undergo progressive enlargement. Keith and Brick[3] showed that changes in the size of the heart did not depend upon the nature of valvular lesions. Taussig and Keith showed that cardiac enlargement occurs during periods of active rheumatic infection and the rate of change is partly related to the added load placed upon the heart during these periods. Taussig[7] also pointed out that once infection has subsided and the heart has adjusted itself to the valvular lesion, no further increase in size of the heart occurs, other than that which is commensurate with normal growth. Furthermore, of the patients studied by Taussig and Keith, all who showed progressive cardiac enlargement had signs of persistent infection. Bland[1] concurs in this statement and states emphatically that to this statement there is not a single exception. Infection may be present without cardiac enlargement[7]. This fact indicates that cardiac enlargement depends not only upon the severity and duration of the disease but, also, in many instances

upon the work demanded of the diseased heart.

Palmer's[4] classic paper, already cited, comes to the same conclusions for the adult. Gross[5] states, "The occurrence of heart failure in the first five decades of life in individuals who have a valvular defect can, in the majority of instances, be attributed to an active infection of the myocardium rather than to the degree of the mechanical defect." The high frequency of reports positive for active rheumatic carditis from biopsies of the left auricular appendage and the subsequent course of events in many individuals subjected to mitral commissurotomy confirm the presence of smouldering subclinical active rheumatic carditis[6-8]. It is most important that the past observations of many astute students of rheumatic fever should not be forgotten during the present enthusiasm for the surgical treatment of rheumatic valvular lesions.

Indeed, the roentgenologic findings, following mitral commissurotomy, force us to the inescapable conclusion that mitral commissurotomy imposes, in some way, an additional load upon the heart, to which, fortunately, most individuals are able to adjust, but, unfortunately, in most instances, at the expense of a loss of part of the cardiac reserve. The nature of this load is perhaps not as simple or uncomplicated as that which occurs naturally. Some of these factors that may be operative following mitral commissurotomy are as follows:

(1) PERICARDIAL EFFUSION. That pericardial effusion occurs in the immediate postoperative period has been established by (a) postmortem studies in those who died soon after operation and (b) by pericardial tap in those in whom signs of cardiac tamponade occurred. In another communication, we shall discuss the differential diagnosis and significance of pericarditis occurring after mitral commissurotomy. It is our impression that most instances are not simply "traumatic" in origin but have a significant rheumatic component. In any event, pericardial effusion does not explain the residual cardiac enlargement present 6 months after operation. Actually, the persistence of enlargement of the cardiac silhouette that slowly regresses in size appears to us to be significant of an important cardiac lesion independent of the pericardial effusion present in the immediate postoperative period.

(2) SURGICAL PRODUCTION OF MITRAL REGURGITATION. The idealized diagram used by the surgeon to depict his operation as making linear incisions in fictitious commissures followed by complete closure of the mitral valve represents an ardent longing rather than an accomplished fact. We believe, on the contrary, that the production by mitral commissurotomy of mitral regurgitation is very common, if not universal. Of the 20 patients forming the basis of this report, only 4 had a definite apical systolic murmur before operation. In all 4, the systolic murmur became more prolonged and more intense after operation. Thirteen of the 20 patients developed a systolic murmur for the first time after operation. Four had a regurgitant jet that was increased by surgery. Of the 17 with postoperative systolic murmurs, 10 had larger cardiac silhouettes, 3 were unchanged and 4 were smaller. None of those that were larger had an uncomplicated course. Our impression, at this time, is that the systolic murmur is indicative of mitral regurgitation. If mitral regurgitation is excessive, severe congestive failure occurs quickly and may be fatal. Otherwise, the myocardium, in the absence of complications, compensates for this new lesion and

adjusts itself without recognizable enlargement.

(3) ATRIAL FIBRILLATION. Fibrillation that follows mitral commissurotomy does produce cardiac enlargement. But, the enlargement, in the absence of complications, is prevented from progressing and is quickly removed by digitalization.

(4) CARDIAC FAILURE. Cardiac failure is not uncommon following mitral commissurotomy. It occurred in 45% of our patients. It usually occurs within 3 weeks after operation and is characteristically right-sided, with rapid gain in weight, a tender and enlarged liver, and slight to moderate pitting edema of the lower extremities. This type fits in well with roentgenologic evidence of right ventricular enlargement, increased venous pressure and prolonged right heart circulation time. However, in the absence of other complications, an initiation or intensification of a medical regimen for cardiac failure frequently dissipates this manifestation. Of the 9 patients exhibiting cardiac failure, the cardiac silhouette was larger in 6, unchanged in one and smaller in 2.

(5) RHEUMATIC CARDITIS. Of the 20 patients, 12 developed active carditis, 3 with immediate and 9 with delayed onset. Of the 3 with immediate precipitation of rheumatic fever, all developed, within 3 weeks after operation, fever, pericardial friction rub, enlargement of the cardiac silhouette, heart failure, prolonged P-R interval, leukocytosis and elevated erythrocyte sedimentation rate. One with splenomegaly had 2 pericardiocenteses and a total of 210 cc. of serosanguineous fluid were removed without change in symptoms or signs. This one also received adrenocorticotropin with benefit during its administration and relapse upon withdrawal. Heart failure has persisted in one, 10 months after surgery. An aortic diastolic murmur appeared in one who never had this murmur before operation and was intensified in another. One has continued to have bouts of fever and chest pain. Biopsy of the left auricular appendage was positive for Aschoff bodies in 2 of the 3.

Of the 9 with delayed reactivation of rheumatic fever, 4 have been reported in detail elsewhere[6] and 2 others (Cases 1 and 3) are fully described in this report. Of the remaining 3, all had heart failure in the early postoperative period which has persisted in one and re-appeared in another. A pericardial friction rub was audible for 2 to 12 days and the electrocardiogram showed changes consistent with a pericarditis. All have had bouts of fever and chest pain for at least 6 months following operation. One was permanently converted to atrial fibrillation. In one, an aortic diastolic murmur appeared after operation and remains audible, at present, 9 months after operation. Biopsy of the left auricular appendage was positive for Aschoff bodies in one of these 3. The 3 with immediate precipitation of rheumatic fever had the largest cardiac silhouettes following operation, had the slowest recession and ultimately developed the largest postoperative increase in cardiac size. Of the 9 with a delayed onset of rheumatic activation, 4 had larger cardiac silhouettes, 2 were unchanged in size (one of these is now larger one year after surgery) and 3 were slightly smaller. All, however, appeared to have a much slower recession of heart size than those who did not develop either rheumatic activation or permanent increase.

From these findings, we are inclined to believe that permanent cardiac enlargement may be due, in an occasional instance, to the surgical production of marked mitral regurgitation but, in most instances, is due to precipitation

or reactivation of rheumatic fever (7 of the 11 with larger cardiac silhouettes in our series). Rheumatic carditis would best explain the generalized cardiac enlargement and the predominant failure of the weaker right ventricle. It is, indeed, fortunate that, in most instances in the adult, rheumatic carditis is indolent and that the heart is able so often to adjust to the load imposed by surgery, but frequently at the expense of a loss of part of its reserve.

Summary and Conclusions. 1. Serial roentgenologic studies were made of 44 consecutive individuals subjected to mitral commissurotomy. Of these 44, 7 died and 17 could not be followed roentgenologically for a minimum of 6 months following surgery principally because of geographic reasons.

2. Of the remaining 20, 11 had larger cardiac silhouettes, 4 were unchanged and 5 were smaller.

3. In this series, there is no roentgenologic evidence that mitral commissurotomy can produce a decrease in the size of that part of the cardiovascular system proximal to the obstruction.

4. The minimal universal diminution in cardiac size which occurred after commissurotomy in 5 of the 20 patients, is attributed principally to a natural remission from a preoperative event precipitating heart failure.

5. The surgical production of mitral regurgitation in rare instances may produce permanent cardiac enlargement.

6. Cardiac enlargement following mitral commissurotomy is attributed primarily to an intensification or reactivation of rheumatic carditis.

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ORAL PROCAINE AMIDE TREATMENT OF HUNTINGTON'S CHOREA

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Despite earlier references, hereditary chorea was not generally recognized until George Huntington's description in 1872[3]. Briefly, the disorder, as characterized by Huntington, consists of the familial occurrence of progressive mental deterioration and involuntary choreiform movements which begin in adulthood. The limits of the disorder have been expanded somewhat from the original description, but the essential features remain as listed.

Although the disease can be diagnosed readily in most instances, there is unfortunately no satisfactory way to suppress its symptoms or to deter its almost inevitable progression. When the involuntary movements have become extremely violent, palliation by pyramidotomy or pedunculotomy may be helpful in a very few selected cases. In general, however, surgery is better utilized in nonprogressive disorders with unilateral involuntary movements rather than in progressive, bilateral conditions such as Huntington's chorea.

Drug therapy also has been unsatisfactory, and there is no drug of proven value for treatment of Huntington's chorea[1]. The belladonna group, traditional for Parkinsonism, has failed in chorea. Although a favorable report on the use of Bulgarian belladonna (Rabellon) in 2 patients appeared in 1947[5], it could not be substantiated by another study reported by a different author[4]. More recently, successful use of oral procaine amide (Pronestyl) has been claimed[2]. Since no subsequent reports have appeared on the use of oral procaine amide, we wish to report herein the result of our trial of this drug.

Material. Ten patients with long-standing chorea were chosen. Nine of these were definite cases of Huntington's chorea, while one was classified as senile chorea. The nosology of senile chorea is disputed, but our patient (Case 10) also had mental deterioration and a suggestive family history, so is probably rightfully included. Since all patients had been hospitalized for some time previous to therapy, environmental conditions were stable. All patients were normotensive, all had negative serologic tests for syphilis, and all were free from other systemic or neurologic disease.

Case Reports: case 1. M.T. is a 44-year-old man, in whom ten years ago slight involuntary movements began. There were no mental symptoms except seclusiveness. His mother, aged 66, was living and well. The father, who died at the age of 44, had suffered from insanity and nervous movements. The father's brother committed suicide at the age of 60 because of involuntary movements. A sister, aged 22, has involuntary movements. The patient's movements affect mainly his head and trunk, a so-called "head-bobber." His extremities are affected to a lesser extent. His gait is slow, broad based, and progression delayed by slight pauses and hesitations.

case 2. G.C., a woman aged 53, was hospitalized 13 years ago because of paranoid delusions. Her grandmother died in a mental hospital. One brother (Case 3 below) has

chorea. The patient is confined to bed, does not speak or walk. She has constant irregular, nonrhythmic nodding of the head, twisting of the trunk, flexion of wrists, grimacing, and twitching of the legs.

CASE 3. L.B., a 44-year-old man, suffers from moderate confusion and complete inability to care for his personal needs. He is a brother of Case 2. He has slow, mild choreiform movements of head, arms, and legs. His gait is hesitating, interrupted every 1 or 2 steps by sudden dysmetric stride.

CASE 4. M.R., a 63-year-old woman began to have violent temper tantrums 27 years ago. Two of her grandparents died with mental deterioration. One uncle was institutionalized. The patient's brother has chorea (Case 5). She displays marked ambivalence to examiners; cooperative on some occasions, irascible at other times. She has grimacing, head nodding, and irregular, nonrhythmic slow movements of her extremities. She is unable to walk.

CASE 5. L.S., a 63-year-old man, is markedly obtunded mentally, and unable to follow a conversation. He is a brother of Case 4. He has moderate choreiform movements of the entire musculature, but is able to walk with some assistance.

CASE 6. J.H., a 58-year-old man, is well oriented and cooperative but childishly stubborn. There is no family history of chorea, but the patient does not know his full background. He has frequent slight to moderate movements of tongue, face, and extremities. He also has a lurching gait, interrupted every 3 or 4 steps by sudden bizarre elevation of the legs requiring a quick shuffle to regain balance. His speech is interrupted by sudden gasps and grunts.

CASE 7. G.E., a 47-year-old woman, has inappropriate behavior and emotional lability. Her mother and one brother suffer from nervous movements and mental deterioration. She has very slight involuntary movements of her extremities, and frequent grimaces. Her gait is nearly normal, but interrupted occasionally by shrugging her shoulders and dysmetric stride.

CASE 8. A.H., a 42-year-old woman, is mentally deteriorated but is able to follow a conversation. Her grandfather and 3 aunts had nervous twitching. She has frequent, almost constant movements of her face, head, trunk, and body. She also has a reeling gait, and is grossly unsteady.

CASE 9. N.W., a 67-year-old woman, has moodiness and paranoid delusions. Her grandmother, aunts, and brother suffered from insanity and nervous movements. She has severe and incessant choreiform movements of entire musculature; gait lurching, reeling and is grossly unstable. Occasionally a particularly strong movement tosses the patient to the floor.

CASE 10. W.M., an 89-year-old man began, at the age of 80, to have temper outbursts and uncontrolled movements. His father and mother died at the age of 50, cause of death, unknown. His sister and brother died in middle age of unknown cause. One daughter has been in a mental hospital for the last 10 years. The patient has moderate choreiform movements of face and extremities. He can walk when aroused but remains in bed most of the time. His gait shows the usual skips and hesitations of chorea.

Method. Prior to starting medication, the type and extent of the involuntary movements were noted and motion pictures taken with special attention to the gait. We attempted to devise several simple standardized tests, such as tying shoestrings and copying a short paragraph, but in general even these simple tasks were beyond the patients' abilities. Final judgment was based on motion pictures and frequent clinical observation before, during, and after medication.

We began treatment with 0.25 gm. of Pronestyl 4 times daily, increasing the dosage by 0.25 gm. q.i.d. every 6 days until a maximum dose of 1.0 gm. q.i.d. was reached. The maximum dose was maintained for 2 weeks in every case except Case 4 where medication was discontinued because of nausea and vomiting after 10 days of full dosage. The total period of medication was 6 weeks, and the total period of observation was 12 weeks. We had originally planned to follow up the trial period with placebo control, but our results did not warrant this.

Results. No improvement could be detected in any of the patients. The movements continued at the premedication frequency and amplitude, and ability to perform coordinated motor acts was unchanged. In no case was the gait improved. In some instances certain patients would seem improved on one visit only to return to their former state or to be worse at the next. Sudden withdrawal of medication produced no exacerbation.

A rather striking feature was the

subjective response. The 7 patients out of the group who were rational enough to be communicative stated unequivocally that they had been greatly benefited by the medication.

Summary. Nine patients with Huntington's chorea and one with senile chorea were treated with oral procaine amide in maximum dosage of 1.0 gm., 4 times a day. Subjective responses were uniformly favorable, but there was no observable improvement in gait or muscular control, and there was no suppression of choreiform movements. We are unable to confirm the efficacy of oral procaine amide in Huntington's chorea as previously reported by another author[2].

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STUDIES ON THE SULFHYDRYL CONTENT OF HUMAN LEUKOCYTES AND ERYTHROCYTES*

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Glutathione, (GSH), has long been implicated as a factor necessary for cell division and consequently might be expected to play a role in the rapid proliferation of leukemic tissue and of marrow tissue in certain of the anemias. It is known, for example, that the addition of free sulfhydryl (SH) containing compounds such as cysteine and glutathione prevents the differential inhibition of cell division without loss or inhibition of cell growth resulting when sublethal concentrations of penicillin are added to yeast cultures[16]. In the absence of added SH, yeast cultured in this environment elongate into filaments but do not undergo normal cell division. The effect is prevented by maintenance of an adequate GSH concentration and ratio of reduced to the oxidized form. Free sulfhydryl also appears to have a relationship to the activity of carcinogens[7]. When 3:4 benzopyrene is incubated with SH there is a change in the physical and biologic properties of the carcinogen. It is no longer carcinogenic and its fluorescent spectrum is altered. In the metabolism of the benzopyrene it appears that detoxication and carcinogenesis occur together and that SH is involved. Investigation of other hydrocarbons shows reactions similar to the benzopyrene among the carcinogens but not among the non-carcinogens. A drop in plasma SH lasting up to 6 hours has also been noted in dogs and rabbits after a single injection of 5.0 mg. of 3:4 benzopyrene[23].

Tissue and plasma GSH levels have been investigated after the induction of tumors in animals. In one study[14] on rats injected with 1,2-5,6 dibenzanthracene, there was an increase in the liver GSH 9 months after the first of 3 bimonthly injections. Assays were done on the sarcomatous nodules which developed, as well as on liver dissected

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free of these nodules. Increased values of GSH in the livers of injected animals were noted when the values were compared with control rats that had not received the hydrocarbon. The tumor tissue, however, contained considerably less GSH than the surrounding liver tissue, and also less than the livers of the control animals. It was felt from this study that the increase in liver GSH was a late effect of the carcinogen since these hydrocarbons are rapidly eliminated.

The effect of the Murphy-Sturm Lymphosarcoma on plasma SH in rats has been investigated by Shacter *et al.*[20] employing the amperometric method of assay. In this type of tumor transplant there is an initial lag phase of tumor growth for about 6 days, then a rapid growth or logarithmic phase until a maximum size is reached at about the 15th day. The tumor then declines rapidly until it is virtually absent by the 23rd day. Following the injection of the foreign protein (tumor) there was an initial drop in plasma SH followed by some increase in the lag phase of tumor growth during which normal values were not reached, however. In the logarithmic phase of rapid tumor growth there was a drop in the SH coincident with the increased mitotic activity of the neoplasm. As the tumor regressed after the 16th day there was again a rise in the plasma SH so that by the 23rd day it was nearly normal. The authors concluded that the experiments "lend support to the concept that decreases in plasma SH levels are a reflection of markedly increased utilization of SH groups by tissues". While this study is certainly highly suggestive of an increased utilization of plasma SH by tumor tissue, it would not necessarily indicate an increased rate of SH consumption or utilization per individual tumor cell.

Woodward[24] studied rats with Walker No. 256 carcinoma and Philadelphia No. 1 sarcoma, but did not find any change in the GSH content of tumor tissue assayed by the glyoxalase method. The author noted that care must be taken in sampling the tumor, since GSH as well as ascorbic acid was present only in samples taken from actively growing areas, but virtually absent in the necrotic portions. The GSH content of paired tumors in which retardation of growth of one of the neoplasms was produced by irradiation was studied. During the period of retardation of growth the GSH was decreased but as the tumor resumed its rapid growth the GSH content returned to normal. In tumors resistant to Roentgen-ray this decrease in GSH was not noted.

Kracke[17], in 1936, suggested that GSH may be involved in various hematologic diseases. In rabbits made leukopenic by the injection of benzene there was a drop in the GSH of the bone marrow and blood prior to the onset of the leukopenia. This fall in GSH was considered as possibly due to its oxidation by one of the degradation products of benzene. It was surmised that the leukopenia was due to depletion of a normal acceleration factor for cell division presumed to be GSH.

Bichel[3] using the iodometric method for assay of GSH noted increased values in whole blood in patients with chronic lymphocytic and myelocytic leukemia. In animals made leukopenic by benzene and Roentgen-ray, Kracke's observations were not confirmed in that no reduction in GSH could be demonstrated. In hemorrhagic anemia no correlation of GSH and reticulocyte count was observed.

In 1950, Contopoulos and Anderson[8] reported on the GSH concentration of erythrocytes and leukocytes in

normal adults and patients with various disease states. In patients with leukemia they noted a marked increase above normal in the leukocyte GSH concentration and felt that the assay of GSH might be of use in those cases of leukemia which presented diagnostic problems. The study included 3 patients with chronic lymphocytic leukemia, one with acute lymphocytic leukemia, 4 with chronic myelocytic leukemia, and one with agranulocytosis. All of the patients showed abnormal values of GSH and during control of the dyscrasia GSH values approached normal. The greatest GSH leukocyte value was found in the patient with acute lymphocytic leukemia. Elevated leukocyte GSH content was also found, however, in both chronic lymphocytic and myelocytic leukemia while in a granulocytopenic aplastic anemia subnormal values were noted. These authors expressed both erythrocyte and leukocyte GSH values in terms of 100 gm. wet weight of the respective cells. In most patients with leukemia studied, the erythocyte GSH content was also found to be high.

Glutathione has also been studied with particular reference to certain anemias. In patients with pernicious anemia decreased whole blood GSH values have been observed[13]. These returned to normal after therapy with vitamin B_{12}. In rats given a diet deficient in vitamin B_{12} a similarly low GSH concentration was noted which returned to normal after administration of the vitamin. In animals deficient in folic acid and iron, similar reductions were not observed. An increase in blood GSH per unit of hemoglobin has been reported in sickle cell disease[12].

In view of the above data, it was considered of interest to extend the observations of Contopoulos *et al.*[8] on the GSH content of human leukocytes and erythrocytes in normal subjects and subjects with disease. Particularly, the possibility of abnormal GSH concentrations in the cells of patients with leukemia seemed worthy of further exploration.

Methods. A modification of the nitroprusside method was used for all GSH determinations. The separation of leukocytes and erythrocytes of the blood was accomplished by erythrocyte sedimentation using Armour's Bovine Fibrinogen with citrate, (Fraction I) as previously described[6,10,22]. The blood was brought to the cold room (3 to 5° C.) within 20 to 30 minutes after venipuncture and all subsequent manipulations were done at 3 to 5° until the final reading in the spectrophotometer. Since heavy metal ions catalyze the oxidation of GSH, the chelating agent sequestrene (disodium ethylenediaminetetraacetate) was added to the fibrinogen saline solution. After 20 minutes, sedimentation of the erythrocytes permitted the aspiration of the leukocyte-rich plasma supernate which was then centrifuged at 1000 RPM (250 G) for 5 minutes to minimize platelet contamination. A red cell-rich suspension almost completely free from white cell contamination was prepared from the erythrocytes at the bottom of the sedimenting tube.

Since it has been previously noted that plasma does not contain GSH[4,13] the centrifuged cells were not washed, but suspended directly in saline.* The only exception to this was in patients with diabetes mellitus. Ketone bodies may possibly interfere with the nitroprusside reaction, and consequently both red and white cells were washed twice with 0.9% saline. Triplicate red and white cell counts were done on each suspension. The suspensions were centrifuged for 10 minutes at 2500 RPM, (1500 G) the saline was aspirated and the cells resuspended in an equal volume of glass distilled water. The erythrocytes were thus lysed with release of their GSH content. Homogenization for 4 minutes in a tight fitting lucite[5] homogenizer was necessary to effect release of the leukocyte GSH content, since lower values were obtained without adequate homogenization. Appropriate aliquots of the lysed red cell solution and the white cell homogenate were deproteinized by adding 2.0 cc. of 6% HPO_3 in saturated NaCl with sequestrene present

*GSH concentrations of both erythrocytes and leukocytes from the same suspension remained the same after two washes with 0.9% saline.

in a final concentration of 3×10^{-5}M. The duplicates were then supersaturated with NaCl and centrifuged for 20 minutes at 3000 RPM (2200 G) and the supernatant fluid was filtered through No. 50 Whatman filter paper. Spectrophotometer cuvettes containing 6.0 cc. of a saturated solution of NaCl were placed in an ice bath and 2 cc. aliquots of the above filtrates were transferred to the cuvettes. The final color development was obtained using the nitroprusside method as described by Grunert and Phillips[11]. The latter noted that with increasing temperatures the developed color faded more rapidly. Consequently the cuvettes were kept immersed in an ice bath until read. The unknowns were read against blanks which contained 2.0 cc. of 2% HPO_3 in saturated NaCl instead of the cell filtrate. When whole blood GSH values were done, the method described by Grunert and Phillips[11] was employed.

A standard was prepared by dissolving 20 mg. of GSH in 100 cc. of 2% HPO_3 in saturated NaCl. It was found that the standard was stable when stored at $-17°$ C. without noticeable oxidation over a 3-month period. In plotting the standard curve with concentrations varying from 20 to 200 micrograms, the curve started at the zero point and followed the Beer-Lambert Law. All tissue concentrations for both erythrocytes and leukocytes gave readings which were within this range. The final reading was made in a Model B. Beckman Spectrophotometer at 520 millimicrons wave length. Two standards were done daily using 100 micrograms GSH. Good agreement in results was obtained with an error less than 3%. To test the recovery of GSH in a cellular filtrate, GSH in HPO_3 was added to the cellular filtrate at the stage of protein precipitation, and the determination completed as described. The added GSH was recovered in 91.5 to 95% yield.

All values for GSH concentration in the subsequent data are expressed as mg. per 10^{10} cells. The erythrocyte GSH content was calculated directly since leukocyte contamination of the erythrocyte-rich suspension was negligible. However, erythrocytes were present in sufficient concentration in the leukocyte-rich suspension to require correction for their presence. This was done by subtracting the GSH contribution of the erythrocytes in the leukocyte suspension as calculated from the unit cell erythrocyte GSH.

The nitroprusside method was used because of its relative specificity and the lack of interfering substances influencing the reaction. Cysteine was the only substance tested which gave an increased value with this method. Ascorbic acid added to a GSH standard and ergothioneine and sequestrene added to cell filtrates did not show interference. No interference was noted from a cell-free plasma fibrinogen solution.

Other methods were also studied for assay of reduced GSH. The iodometric method[25] gave good duplicate checks, but because of lack of specificity it was not used. In this method both ascorbic acid and ergothioneine gave increased values when added either to a GSH standard or a cellular filtrate.

A titrimetric glyoxalase method[19] did not give us reproducible data with either a GSH standard or with a cellular filtrate. A further modification of this method was tried in which residual methyl glyoxal was measured by formation of an osazone[15]. The osazone was dissolved in sodium ethylate and the color production measured in the spectrophotometer. However, suitable duplicate checks could not be obtained consistently and the method was abandoned.

Results. NORMAL SUBJECTS. Twenty-two pre-operative patients of varying ages were selected. These patients were in good health and had entered the hospital only for elective surgery, that is, hernia and varicose veins, which would not preclude normalcy. The leukocyte GSH values showed a rather marked range, varying from 3.3 to 6.3 mg. with an average of 5.1 mg. The majority of the values were between 4.5 and 6.0 mg. The erythrocytes showed less variation, ranging from 0.44 to 0.90 mg. with an average of 0.72 mg. Only one value was below 0.50 and only 4 were below 0.60 mg. The data indicate that the reduced GSH concentration of normal leukocytes on a cell for cell basis is much higher than that found in normal erythrocytes, the ratio being approximately 7:1. Studies on whole blood compared with previous reports[2,21]. Erythrocyte and leukocyte GSH values for normal subjects and subjects with various disease states subsequently discussed are shown on a scattergram in Figs. 1 and 2.

NEUTROPHILIC LEUKOCYTOSIS. Thirty-five subjects were studied in this group.

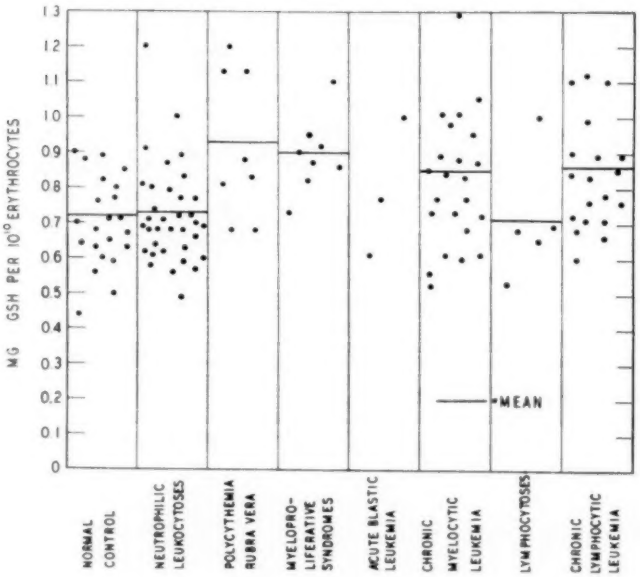

Fig. 1.—Scattergram indicating mg. of GSH per 10^{10} erythrocytes in normal subjects and patients with various disease states.

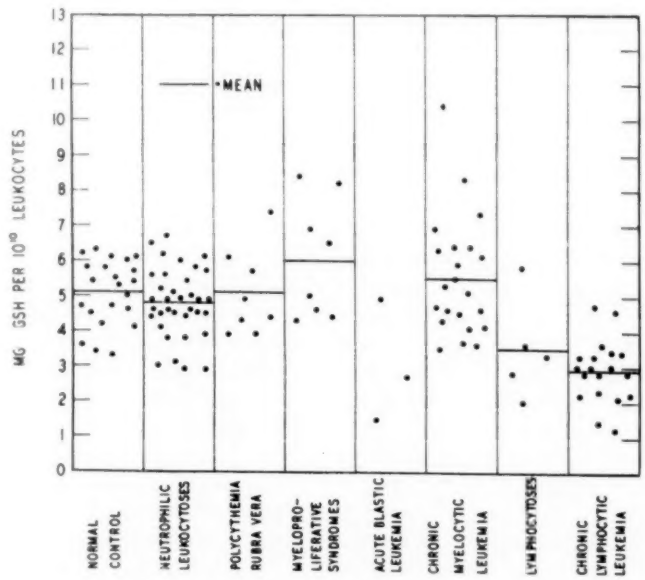

Fig. 2.—Scattergram indicating mg. of GSH per 10^{10} leukocytes in normal subjects and patients with various disease states.

These were divided into leukocytoses secondary to infection and those secondary to such non-infectious pathology as, for example, myocardial infarction. The values were essentially normal in both groups. Values in cases with infection varied from 2.9 to 6.8 mg. with an average of 4.8 mg. per 10^{10} leukocytes, and only two were 3.0 mg. or less.

The lowest was 2.9 mg. in a patient with disseminated coccidioidomycosis who also had an eosinophilia of 14.5%. The other low value of 3.0 mg. was in a patient with chronic ulcerative colitis whose differential leukocyte count showed a prominent shift to the left including myelocytes in the peripheral blood.

In the non-infectious leukocytoses there was a comparable range of leukocyte values averaging 4.9 mg. with only two determinations of 3.1 mg. or lower. The lowest value of 2.9 mg. was found in a patient with uremia. One other low value of 3.1 mg. was found in a patient with carcinoma of the kidney with metastasis, whose differential formula showed a marked shift to the left with 15% myelocytes in the peripheral blood.

LYMPHOCYTOSIS. Four patients with infectious mononucleosis in various stages of their disease and one with a lymphocytosis associated with myocarditis were studied. In the cases of infectious mononucleosis the lymphocytes constituted 77 to 81% of the cells. In the case of myocarditis, the lymphocyte percentage was 59%. The lowest GSH value was 2.0 mg. in a patient with infectious mononucleosis who showed 77.5% lymphocytes by differential count. All values with one exception were low or low normal, the exception being 5.75 mg. in a patient with infectious mononucleosis studied during early convalescence but who still showed 81% lymphocytes in the peripheral blood. On a cell for cell basis it may be concluded that the leukocyte types analyzed in these cases are relatively poor in GSH measured by the nitroprusside method.

POLYCYTHEMIA RUBRA VERA. Eight determinations were done on 6 patients. Leukocyte GSH ranged from 3.9 to 7.4 mg. and averaged 5.1 mg. Only one value was found above the normal range. Leukocytosis was present in all but one patient, and with the one exception there was an increased neutrophile percentage as well as a shift to the left in the differential formula. While 3 patients had received either P_{32} or Roentgen-ray, none had received this therapy for several months prior to these studies.

"MYELOPROLIFERATIVE SYNDROMES"[9]. These patients were characterized by unexplained non-leukemic peripheral leukocytosis in all but one patient whose total leukocyte count was normal. The peripheral blood showed immaturity of the myeloid elements including blasts in several cases. Anemia was present in almost all instances, as well as splenomegaly and hepatomegaly. Eight determinations were performed on 5 patients. Erythrocyte GSH was found to be elevated or at the upper limits of normal; ranging from 0.73 to 1.10 mg. and averaging 0.90 mg. Leukocyte GSH was normal or moderately elevated with an average of 6.0 mg. and a range of 4.3 to 8.4 mg.

LYMPHOCYTIC LEUKEMIA. Nineteen determinations were done on 13 patients. These studies during remission or exacerbation, before, and during therapy showed leukocyte GSH values that were almost universally low or low normal. The range was 1.2 to 4.7 mg. with an average of 2.9 mg. as measured by the nitroprusside method.

One patient was followed at weekly intervals during a course of Roentgen therapy. There was essentially no

change in either erythrocyte or leukocyte GSH despite hematologic remission and an 8-fold reduction in leukocyte count. It is of interest that one determination was made 45 minutes after the third Roentgen-ray treatment and failed to show any immediate effect of irradiation. Another patient was studied at the time of entry to the hospital when he was rather acutely though not critically ill, and had a leukocyte GSH content of 2.1 mg. After he had received Roentgen-ray treatments along with transfusions and showed considerable clinical as well as laboratory improvement, leukocyte GSH was still only 2.75 mg. No consistent effect of therapy on the GSH leukocyte content could be found in these subjects therefore.

In chronic lymphocytic leukemia only two patients showed values above 3.6 mg. in leukocytes. One was studied during convalescence from pneumonia at which time his leukocyte count was 5600 per c.mm. with 77.5% lymphocytes. A few months earlier it had been 200,000 per c.mm. and had dropped to the present level after a course of Roentgen therapy. His leukocyte GSH was 4.7 mg. A leukocyte value of 4.6 mg. was found in another patient who was asymptomatic at the time of study. The leukemic lymphocyte, cell for cell, exhibited lower GSH content than the cells of normal subjects.

MYELOCYTIC LEUKEMIA. Twenty-one determinations were done on 10 patients. Here the leukocyte GSH showed a greater spread than in any other disease state studied. The values ranged from 3.5 to 10.4 mg. with 5.5 mg. as the average leukocyte GSH. Five of the patients showed transient elevations but were otherwise normal, 4 other patients were within normal limits at all times, and the tenth patient showed on only one occasion a value very minimally above the normal range. There was no consistent correlation of the GSH to remission or exacerbation of the disease or to irradiation. One patient on entry to the hospital had a leukocyte count of 607,000 per c.mm. Erythrocyte GSH was 0.95 mg. and leukocyte GSH 6.3 mg. at this time. One week after the last Roentgen-ray treatment he was clinically much improved, and had a total leukocyte count of 4200 per c.mm. At that time the erythrocyte GSH was 0.84 mg. and leukocyte GSH 5.3 mg. Another patient was studied at the onset of Roentgen therapy and again 4 months after it was completed. Leukocyte GSH values remained unchanged. The course of two other patients was also followed during a period of Roentgen-ray therapy. In one, leukocyte GSH rose with therapeutic remission while in the other it fluctuated slightly but in an inconsistent manner. The erythrocyte GSH in these subjects remained relatively unchanged throughout therapy.

ACUTE BLASTIC LEUKEMIA. Three patients were studied with single determinations. Two of these patients showed unusually low leukocyte values of less than 3.0 mg., and in the fourth a normal value of 4.9 mg. was obtained.

MISCELLANEOUS. GSH content of erythrocytes and leukocytes was also measured in several disease states other than those recorded above. Two patients with reticulum cell leukemia showed leukocyte GSH of 5.3 and 6.3 mg., both results falling in the normal range. In two patients with leukemoid reactions secondary to carcinoma of stomach and ulcerative colitis slightly elevated leukocyte GSH values of 6.6 and 7.0 mg. were noted. One patient with eosinophilic leukemia showed low values on two occasions of only 3.2 and 2.7 mg. Six determinations were

done on 4 patients with lymphomas other than leukemia. Leukocyte values ranged from 3.1 to 6.6 mg. with an average of 4.4 mg. These findings were both above and below the normal range and did not suggest any trend. Due to the difficulty in obtaining an adequate concentration of leukocytes, only a few patients with leukopenia and anemia were studied. One subject with aplastic anemia and another with a nutritional megaloblastic anemia following gastrectomy both showed a normal GSH concentration in their erythrocytes and leukocytes. The erythrocytes only were studied in one patient with congenital hemolytic icterus and a normal GSH concentration was found. Another patient reported among the chronic myelocytic leukemia group also had sickle cell disease. In this case the erythrocytes showed a GSH concentration in the normal range.

Three patients with diabetes mellitus were studied. All had leukocyte GSH concentrations within the limits of normal. One of them had entered the hospital in acidosis 24 hours before the assay, but was not acidotic at the time of study. However, a well marked leukocytosis was still present. The other two patients were under fair diabetic control and did not exhibit leukocytosis.

Discussion. Comparison directly of the foregoing data with those of previous reports is rendered difficult due to varying techniques and standards of reference in different studies. In this investigation GSH is recorded on a per 10^{10} cell basis while in others values have been expressed in terms of cell wet weight or per cubic centimeter of blood, the latter expression of course ignoring the wide possible variations in cell numbers and types in pathologic states. However, summation of leukocyte and erythrocyte GSH content in normal subjects and conversion of this value to the content of GSH present in the cells of one cubic centimeter of the subject's blood indicate good correlation with data from our own and from other sources recording whole blood GSH content[2,21]. While the great portion of blood GSH is found in the erythrocytes because of their much greater mass, on a cell for cell basis leukocytes were found in this study to contain 7 times as much as red cells. This ratio is much higher than that noted by Contopoulos[8]. The reasons for this are not clear although we have found it necessary to actively homogenize leukocyte suspensions to obtain satisfactory GSH release for assay. If the assumption is made that 10^{10} leukocytes represent approximately 4.0 gm. wet weight of this tissue[18], then in normal subjects the leukocyte GSH content is on the average 1.25 mg. per gm. wet weight of tissue. This compares favorably with Woodward's[24] findings in other tissues. For example in rats she found that liver contained 1.72 mg.; adrenal, 1.09 mg.; spleen, 0.92 mg.; and kidney, 0.77 mg. when the glyoxalase method for assay was used.

In contrast to the observations of Contopoulos and Anderson[8], elevated values of leukocyte GSH were not observed in a rather large group of leukemic subjects and no consistent change in these values accompanied radiation therapy with good hematologic response. In chronic myelocytic leukemia, values showed no consistent trend but ranged from low normal to moderately elevated. One patient followed during Roentgen-ray therapy showed gradually increasing leukocyte GSH values while in others there was either no change or an insignificant reduction. In the cases studied the levels of leukocyte GSH were comparable to those in many normal subjects or to those in subjects with other disease

states and were not diagnostic. No essential differences were noted from values obtained in non-leukemic myeloproliferative syndromes or in polycythemia rubra vera.

In chronic lymphocytic leukemia and in the acute blastic leukemias, leukocyte GSH was almost uniformly low and in a patient with chronic lymphocytic leukemia, followed through a course of Roentgen-ray with good therapeutic response, the GSH values of both erythrocytes and leukocytes remained unchanged. The low values may be related to cell type but also may be related to average cell size. In this laboratory[1] the leukocytes of chronic lymphocytic leukemia on a per cell basis have been found to have on the average something less than half the nitrogen content of leukocytes of normal blood and those of chronic granulocytic leukemia. Expression of GSH content on the basis of cell nitrogen would, therefore, give normal but not elevated values in chronic lymphocytic leukemia. Moreover, roughly comparable low values of GSH were observed in the lymphocytoses of infectious mononucleosis so that it does not appear from these data that the leukemic lymphocyte differs sharply in GSH content from the lymphocyte of certain benign pathologic conditions.

Erythrocyte GSH showed little variation in any of the diseases studied. Except for a few random samples that showed a slight increase, a consistent trend toward elevation was found only in the myeloproliferative syndromes. Erythrocyte GSH on a per cell basis was not affected by therapy in any disease where this was studied.

It may be concluded that in these studies on the GSH content of isolated leukocytes and erythrocytes no clear-cut trend was apparent to relate the free sulfhydryl content of the cells to either increased myelopoietic or erythropoietic activity. Sulfhydryl levels in the leukocytes under conditions of intense myelopoietic activity such as leukemia, myeloproliferative syndromes, and infection were for the most part within the normal range. The exceptions of low values in chronic lymphocytic leukemia, blastic leukemia, and infectious mononucleosis may be inherent for the cell types analyzed or may be due to differences in mean cell size. Erythrocyte GSH showed a tendency to be a little above normal in the myeloproliferative syndromes but the range of GSH content did not appear to vary widely in the pathologic conditions studied.

Summary. A brief review of the relationships of glutathione and other sulfhydryl compounds to cell proliferation, to certain hematologic conditions and to certain malignant states is presented. The glutathione content of separated leukocytes and erythrocytes in health and disease has been measured by the nitroprusside method and expressed as mg. of GSH per 10^{10} cells. The data obtained in this study indicate (1) the ratio of leukocyte to erythrocyte GSH in normal subjects is approximately 7:1; (2) by the aid of an assumption relating leukocyte numbers to wet weight leukocyte GSH concentration is comparable to that observed for many other body tissues; (3) by the method employed elevated GSH values have not been found to be associated with the leukemic state and, in fact, the per cell values in blastic and in chronic lymphocytic leukemias have been found consistently low; (4) low per cell GSH content is also observed in the lymphocytosis of infectious mononucleosis, an observation which may be related to cell type or to a lower average cell size in the case of lymphocytes; (5) no clear-cut relationship of free sulfhydryl content of cells

to either increased myelopoietic or erythropoietic activity in various nonleukemic states has been observed; (6) erythrocyte GSH has shown little variation from normal in the variety of disease states studied.

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THE PATHOGENESIS OF INFECTIOUS MONONUCLEOSIS

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PUBLISHED articles on infectious mononucleosis have become so numerous that it would be difficult, and perhaps not very profitable, to attempt any thorough review of them here. Bernstein's monograph[8] summarizes in a careful and detailed manner the various articles published up until 1940. Since then there have been numerous reviews connected with some particular aspect of the disease, as well as general reviews such as those of Wechsler[65], Wising[67], and Sohier[60]. The excellent short summary by Gardner and Paul[32] of the clinical features of the disease should be listed also as a valuable reference. It is particularly appealing because of the fact that it is concise and clear, in contrast to some of the articles on infectious mononucleosis which trend toward the opposite.

In general there appears to be increasing realization that infectious mononucleosis is a disease with a great variety of clinical manifestations, as indicated by the almost hackneyed use of the word "protean" in describing its clinical features. In addition, the increasing information on visceral lesions, obtained from necropsies, even though their number is still not great, demonstrates that the lesions of the disease are widespread throughout the body. The clinical features of the illness will not be discussed here in detail, but will be reviewed rather quickly from the standpoint of the concept that infectious mononucleosis may represent a disease of hypersensitivity, rather than a specific infection in the usual sense of the term. Therefore, somewhat greater attention will be given to the hematologic and serologic abnormalities, the pathologic picture, attempts to incriminate various microorganisms as causal agents, and the

theories which have been advanced to explain the disease. With this line of approach, clinical and laboratory studies will not always be sharply separated, and pieces of clinical information may be considered under the various subdivisions of laboratory study which seem to bear on the question of the pathogenesis of the disease. The brief clinical summary will include a somewhat more detailed discussion of the occurrence of hepatitis and of lesions of the nervous system in infectious mononucleosis, in part because reports of such lesions have appeared in increasing numbers since the earlier reviews on the clinical features of the disease. However, there will be no attempt to make these descriptions all-inclusive.

Clinical Features. For a detailed description of the clinical aspects of infectious mononucleosis the reader is referred to the recent reviews, some of which are listed in the introduction. The tendency for the disease to occur in children and young people, and to occur in epidemic form, is stressed by most authors. The clinical picture, on the whole, is one of an acute infection, with fever, sore throat, and enlargement of lymph nodes as its most prominent features. In some patients the picture is dominated by hepatitis or involvement of the central nervous system. The high incidence of sore throat, sometimes with stomatitis, is well known. It is of interest that the cervical lymph nodes are the ones most frequently involved[8,32]. The occurrence of rashes in the course of the disease has been emphasized by Tidy[63].

Hepatitis, with or without jaundice, may occur in infectious mononucleosis, sometimes with considerable clinical and laboratory similarity to infectious hepatitis[17,53,64]. Biopsy and necropsy studies have demonstrated that the lesion is a diffuse hepatitis, but are insufficient to establish the incidence of hepatitis in the disease. Chemical tests of hepatic function show abnormalities in the great majority of patients studied and suggest that involvement of the liver is almost always present[13,14,24]. Tests which are related to changes in the serum proteins, such as the thymol turbidity and the cephalin-cholesterol flocculation tests, should probably be interpreted with caution in infectious mononucleosis, since abnormalities of the serum proteins could conceivably be produced by the hyperplastic lymphoid tissue. In many of the cases reported, however, there has been confirmatory evidence of impaired hepatic function, such as retention of bromsulfalein and elevation of serum bilirubin.

The neurologic complications of infectious mononucleosis are comparatively rare, but there is an increasing number of such case reports. The subject was reviewed in 1950 by Bernstein and Wolff[9], and more recent references are given in the article of Raftery and associates[54]. The manifestations are remarkably varied in regard to their clinical type and time of appearance. Some of the neurologic disorders which have been reported are meningitis, encephalitis, peripheral neuritis, and optic neuritis. The recent reports of the Guillain-Barré syndrome in association with infectious mononucleosis are of particular interest in suggesting a possible allergic basis for the lesions of the nervous system in this disease.

Serologic Abnormalities. HETEROPHIL AGGLUTININS FOR SHEEP CELLS. The presence of heterophil agglutinins in the serum of patients with infectious mononucleosis is of great interest because of its diagnostic value, as well as its possible bearing on the basic nature of the disease itself. In the latter connection, for example, there is at least a superficial resemblance to serum sickness. However, the heterophil

antibodies which are observed in serum sickness and which may occur, in low titer, in normal persons are of the Forssman type and are absorbed by a suspension of guinea pig kidney[16]. This is not true of the heterophil antibodies present in the serum in infectious mononucleosis. For proper evaluation of heterophil agglutinins in regard to the diagnosis of infectious mononucleosis, absorption tests should be carried out unless the titer of antibodies is well past the normal range[42,45].

In Gardner and Paul's[32] series of cases, the percentage of positive heterophil agglutination reactions was greatest during the second week of the illness, thereafter trending downward. As they point out, this has some bearing on the debated subject of whether or not heterophil agglutinins in infectious mononucleosis represent true antibody, since one might expect a true antibody to persist in the serum for longer periods.

A practical point in the consideration of these agglutinins is whether or not their demonstration in the serum at some stage in the disease is necessary for the diagnosis of infectious mononucleosis. It is difficult to evaluate the published evidence in this respect because of lack of adequate description of the test used in many of the case reports. Absorption tests to eliminate antibodies of the Forssman type are not done as a routine procedure, and confusion often results from the failure of authors to state whether the reported titers represent initial or final serum dilutions. The incidence of positive heterophil agglutinins reported in published series varies considerably, but it is probably fair to say that most writers believe that heterophil agglutinins are not always found in the serum in infectious mononucleosis. For example, in Kaufman's series of cases[42], the incidence of positive reactions was 75%. In essence, this comes down to the fact that diagnostic criteria vary among physicians, a point which adds to the difficulty of evaluating published reports. In my opinion, the clinical picture, combined with the presence of large numbers of atypical lymphocytes in the blood, usually represents an adequate basis for the diagnosis of infectious mononucleosis. When, in addition, heterophil agglutinins are found in high or increasing titer and demonstrated to be different from Forssman antibodies, the diagnosis is clearly established.

FALSE POSITIVE TESTS FOR SYPHILIS. Biologically-false positive serologic tests for syphilis are a well-known occurrence in infectious mononucleosis, the reported incidence varying considerably in different published articles[8,68]. Gardner and Paul[32] have pointed out that when such positive tests are found they tend to parallel the rise and fall of heterophil agglutinins in the serum. They are independent of these agglutinins, however, since they persist after the latter have been absorbed by appropriate methods[8]. Saddusk[58] has reported that they have some correlation with the presence of rashes in the disease.

AGGLUTININS FOR RED BLOOD CELLS MODIFIED BY PREVIOUS TREATMENT WITH NEWCASTLE DISEASE VIRUS. This interesting observation, first made by Burnet and Anderson[10], will be discussed here, rather than in the section dealing with the possibility that infectious mononucleosis may be a specific viral disease, because all of the evidence presently available points toward its being an entirely nonspecific reaction. It seems clearly established that a certain percentage of sera from cases of infectious mononucleosis will cause agglutination of human type O red blood cells which have been previously exposed to the presence of the virus of

Newcastle disease. This property, present in low titer in many normal sera, occurs in abnormally high titer in infectious mononucleosis, to a lesser degree in infectious hepatitis, and occasionally in other infectious diseases. The incidence of positive reactions in infectious mononucleosis varies in different series from 25 to 75%, and apparently this variation depends largely on the strain of virus used in the test[23]. Although many sera from cases of infectious mononucleosis contain both heterophil antibody and the agglutinin for red blood cells which have been treated with Newcastle disease virus[23], either may occur without the other, and absorption of one from the serum, when both are present, does not appreciably affect the titer of the other[30]. Since study of the serum in infectious mononucleosis has failed to reveal the presence of any specific antibodies against this virus[26,30], the occurrence of the abnormal hemagglutinin probably cannot be considered to constitute evidence for the theory that there is antigenic similarity between the Newcastle disease virus and the hypothetical virus of infectious mononucleosis.

OTHER ANTIBODIES. Bernstein[8] has reported the occurrence of agglutinins against a variety of bacteria, a finding mentioned in several other reviews of the subject. These agglutinins could conceivably result from the so-called anamnestic reaction. Isoagglutinins for human red blood cells have been described, and there have been a few reports of cold hemagglutinins occurring during the disease[25]. Antistreptolysin titers and the occurrence of agglutinins against *Listeria monocytogenes* will be mentioned later, for convenience, since they may have more direct bearing on theories of the pathogenesis of infectious mononucleosis.

INTERPRETATION OF THE SEROLOGIC ABNORMALITIES. It is difficult to believe that the various abnormalities of the serum described above can be related, in any direct way, to a specific infection. It seems more logical to think that they are the result of the reticuloendothelial hyperplasia which appears to be the basic lesion in the disease. This assumption is consonant with the concept that antibody globulins are formed in the reticuloendothelial system, and it does not imply that the stimulation of such tissues is necessarily caused by a specific microörganism.

Studies of the serum proteins, and especially of the globulin fraction, seem important in such a concept but are complicated by the fact that hepatitis seems to be a frequent feature of infectious mononucleosis. In such a situation it would be difficult, as Sterling[62] has pointed out, to determine the individual roles of the liver and the lymphoid tissue in producing the changes. In Sterling's study of the electrophoretic pattern of serum from 7 cases of infectious mononucleosis, abnormalities were observed in all, without regard to the presence or absence of jaundice. The changes were in the direction of decrease in the albumin fraction and elevation of the gamma globulin fraction. It is of interest that absorption of heterophil agglutinins in these sera did not affect the electrophoretic patterns. With the same line of approach, Evans[25] investigated the serum gamma globulin in infectious mononucleosis, using the turbidimetric technique described by Kunkel[43], and found elevations in turbidimetric units in 41 of 45 patients. Further study of the pattern of serum proteins in this disease might be rewarding, particularly if accompanied by more careful control observations.

Blood Picture. Whether or not the clinician insists on the presence of heterophil agglutinins in the serum as an essential criterion for the diagnosis

of infectious mononucleosis, there seems to be fairly general agreement that the presence, at some time in the course of the disease, of increased numbers of abnormal mononuclear cells is an essential sign. Several authors, including Gardner and Paul[32] and Bernstein[8], have described an initial leukopenia during the first week or so of clinical symptoms, due chiefly to a reduction in granulocytes. The subsequent increase in leukocytes, which generally occurs during the second week of the illness, is the result of an increase in mononuclear cells[8,32,49]. The history of the discovery of these cells in the blood, and the realization that "glandular fever" and "infectious mononucleosis" were the same disease, are of great interest but do not bear upon the present discussion. The most important consideration would appear to be that abnormal mononuclear cells, which occur regularly during some stage of the disease, and usually in high percentages, have considerable diagnostic value and therefore might reasonably be expected to provide some clue to the nature of the disease itself.

At this point, a description of these cells and speculations about their origin would be in order. The unusual mononuclear cells occurring in infectious mononucleosis were described in a definitive manner by Downey[19], in 1923, and no better description appears to have been published since that time. He divided the cells into three types, although he attached no special significance to the division because of the presence of numerous gradations between them, even in the same smear. In the larger cells, cytoplasm tends to be increased and in all of them to be more basophilic than normal. It may also be vacuolated or foamy in appearance. The nuclei of the larger cells are frequently placed eccentrically and generally are irregular or indented. The nuclei of the smaller cells may also be irregular. Nuclear chromatin forms a coarse network of strands. The cells are well illustrated in a color plate in Downey's article. Although there is still some dispute about the nature of the cells, it seems safe to say that most authorities regard them as mature lymphocytes. In addition to the atypical cells just described, the blood contains lymphocytes of normal appearance and also gradations between them and the large pathologic forms[19].

It is of some interest, in connection with the present discussion, that Downey in his earlier report[19], as well as in a later description of the cells[49], stressed their resemblance to plasma cells and suggested that they were intermediate between plasma cells and lymphocytes. This morphologic resemblance is not very striking to me, but it should be mentioned that typical plasma cells may be found in the blood of patients with the disease[49,66]. As will be mentioned later in the discussion of the histologic findings in infectious mononucleosis, there seems to be good evidence that the abnormal lymphocytes originate in the hyperplastic lymph nodes.

Since the atypical lymphocytes are so striking in their appearance and have considerable diagnostic value in infectious mononucleosis, it is important to evaluate reports of their occurrence in other disorders. This is particularly true of their reported presence in viral infections, in view of the widely held theory that infectious mononucleosis is a viral disease. There seems to be little doubt that the cells occur on occasion in infectious hepatitis, but since clinically evident hepatitis may occur during the course of infectious mononucleosis, the diagnosis in some of the reported cases would appear to be a matter for debate. In this connection, the paper of Havens and

Marek[35] is of particular value, since they studied the leukocytic response during the course of experimentally induced infectious hepatitis in human volunteers. They described an early leukopenia with subsequent relative lymphocytosis. During the first week of illness atypical lymphocytes of the sort seen in infectious mononucleosis were reported to be common. The changes in the blood described in this report resembled those occurring in infectious mononucleosis, with the exception that there was no absolute increase in mononuclear cells or long persistence of the abnormal cells in the blood.

Similarly, the atypical cells are said to occur in measles and German measles. The authority for this statement usually given by other authors is the paper of Benjamin and Ward[4]. These authors described the appearance in the blood, during convalescence from measles, of numerous large lymphocytes with the characteristics of young lymphocytes as revealed by supravital staining. They mentioned the occurrence of similar cells in supravital preparations in German measles and infectious mononucleosis. However, they did not make it clear whether or not they considered these large lymphocytes morphologically identical with the typical cell of infectious mononucleosis.

Litwins and Leibowitz[47] have reported the occurrence of the atypical cells in 29 of 55 patients with viral hepatitis, 13 patients with primary atypical pneumonia, apparently of viral origin, 4 patients with herpes zoster, one with herpes simplex, and 2 with roseola infantum. Unfortunately, the clinical information provided is scanty. In none of the diseases mentioned did the number of atypical cells exceed 10%, and they tended to be present in the blood for shorter periods of time than in infectious mononucleosis. Litwins and Leibowitz considered the cells to be morphologically identical with those seen in infectious mononucleosis.

The atypical lymphocytes have been reported by Baldridge and coworkers[2] to occur "in small numbers" in some bacterial infections with associated lymph node enlargement. It is also of interest that they observed the cells in three cases of serum sickness with associated generalized enlargement of lymph nodes. Along the same line, the atypical cells have been reported by Randolph and Gibson[55] in a variety of allergic diseases.

The remaining features of the blood picture in infectious mononucleosis will not be discussed here. Mention might be made in passing of recent reports of instances of thrombocytopenic purpura[1,52] and of acute hemolytic anemia[34] associated with infectious mononucleosis. The mechanism of these complications is not understood thoroughly, and the suggestion that they can be attributed to hypersplenism does not seem to account for all of the clinical information presented.

Pathology. Because of the comparative rarity of necropsy examination in infectious mononucleosis, microscopic study of tissue sections has been concentrated upon excised lymph nodes and fixed sections of bone marrow aspirates. The study of lymph nodes seems of particular interest since they are so frequently enlarged and since they might be expected to throw some light on the source of the atypical lymphocytes which are found in the blood.

LYMPH NODES. There are numerous reports of the histologic study of lymph nodes in infectious mononucleosis, some of them dating from the early days of the clinical recognition and study of the disease. Two more recent studies should be cited as of interest, those of Downey and Stasney[20] and

Gall and Stout[31]. In both of these studies the value of proper fixation and staining of the sections, and of examination of stained smears from imprints of the nodes, is stressed. This appears to be essential for the demonstration in lymph nodes of the atypical lymphocytes which are seen in the blood.

Downey and Stasney[20], in their study of lymph nodes from 6 cases of infectious mononucleosis, described hyperplasia of the reticulum, nodular foci of reticulum cells, compression and distortion of the sinuses, and the presence of large lymphocytes in the sinuses and looser portions of the nodes. There was also hyperplasia of the follicles in a case in which the node was removed at the height of the clinical disease. Imprints of the nodes showed cells identical with those seen in the blood. It is of interest that the authors also stressed the presence of numerous plasma cells in most of the imprints and suggested their origin from lymphocytes.

The report of Gall and Stout[31] derives from a study of ten excised lymph nodes and reviews the previous descriptions of the histologic picture in infectious mononucleosis. It is particularly valuable because it helps to clarify some of the conflicting earlier interpretations and to establish a characteristic histologic lesion of the lymph nodes in this disease. The findings are basically the same as those of Downey and Stasney, although the presence of plasma cells is not stressed. In brief, Gall and Stout describe a proliferation of all of the components of the node, resulting, in the extreme stage, in compression of the sinuses and their packing with lymphocytes and other mononuclear elements, as well as enlargement of the follicles to such a degree that their borders are not clear, but extend in an irregular fashion into the surrounding pulp. This histologic picture is distinguished from other types of hyperplasia by the marked proliferation in the pulp; by focal proliferative activity of clasmatocytes, with morphologic changes; and, most characteristically, by the presence of the specific cell of infectious mononucleosis in the sinuses and throughout the pulp. These characteristic changes produce superficial blurring of the normal structure of the node, but the normal architecture is preserved.

BONE MARROW. The nature of the lesions in the bone marrow has probably been confused in many instances, as Campbell[11] suggests, by attempts to interpret smears rather than fixed sections. In histologic examination of bone marrow obtained by sternal puncture, Campbell observed focal proliferation of mononuclear cells in 12 of 15 cases of infectious mononucleosis. These collections were made up of large cells, resembling undifferentiated reticulum cells, and smaller ones which appeared to be lymphocytes. Some of the latter cells were thought to be identical with the atypical lymphocytes which are seen in the blood. In addition, some of the foci contained small numbers of plasma cells. Campbell considered these foci to be examples of the widespread hyperplasia of lymphoid tissue in this disease. It would seem that the "granulomatous" lesions of the bone marrow in infectious mononucleosis described by Hovde and Sundberg[38] probably are identical with the focal areas of Campbell.

VISCERAL LESIONS. The number of necropsies reported in infectious mononucleosis is small because of the usually benign course of the disease. Reviews of such reports have been presented by Custer and Smith[15] and by Sharp[59]. The former article also gives references to histologic study of the spleen following its removal because of rupture, and of specimens of the liver obtained by

biopsy. The lesions are thought by the authors of both papers to derive locally from stem cells of the reticuloendothelial system. They contain the atypical lymphocytes seen in the blood. The tendency for the cellular accumulations to occur around small vessels is well illustrated in the photographs presented by Custer and Smith. The fact that such lesions may occur in almost every organ of the body provides an explanation for the great variation in the clinical picture of the disease. For example, the occurrence of interstitial infiltrations in the lungs[15,59] is of interest in view of the reported clinical picture of "primary atypical pneumonia" in the course of infectious mononucleosis[57,65]. Similarly, the focal myocardial lesions described by Custer and Smith might account for the reported cases in which there has been clinical or electrocardiographic evidence of myocarditis or pericarditis in the disease[28,50,65]. The hepatic lesion is one of infiltration in the periportal spaces, sometimes with varying degrees of change in parenchymal cells, and is difficult to distinguish from that of infectious hepatitis. Bénazet and associates[3] have recently discussed this subject in detail and have compared the lesions of infectious hepatitis and of infectious mononucleosis in sections obtained by punch biopsy of the liver. They point out that there are important differences between the histologic pictures of the two diseases if the biopsy is obtained early in their course. In infectious mononucleosis there is greater cellular reaction than is seen in infectious hepatitis and much less in the way of changes in the parenchymal cells of the liver.

In the nervous system, perivascular cuffing has been noticed in the substance of the brain and in the meninges[15], as well as radiculoneuritis in the interesting cases in which the Guillain-Barré syndrome has occurred as a complication[36,56].

Observations Bearing on the Concept that Infectious Mononucleosis Is a Specific Infectious Disease. It appears to be the opinion of most students of this disease that it is an infection, probably caused by a virus. The most important piece of clinical evidence in support of this concept is the frequent report of epidemics of the disease. Such reports appear in almost every detailed account of infectious mononucleosis. Epidemics are said to be particularly prone to develop in children and young people in crowded circumstances, such as the environment of a boarding school or dormitory. Several of them were reported in the military services during the last war. Although some of the outbreaks seem to have been genuine epidemics, it appears that in many of them diagnostic criteria were broadened to the point where the reader cannot judge the validity of the diagnosis in many of the patients. This statement is not intended to deny the possibility of asymptomatic cases of infectious mononucleosis or of other unusual clinical features which have been claimed for it. It would appear likely, however, that an outbreak of the disease might well lead to an intensive search for inapparent cases and a loosening of diagnostic criteria. In the absence of exact diagnostic standards, it is obviously difficult to interpret such reports.

Two recent articles are of interest in this respect. Evans[21] made a careful and complete search for asymptomatic cases in a college dormitory after the occurrence of 5 cases of infectious mononucleosis in this setting. No clinical or laboratory evidence of "inapparent infection" was found in the other residents. Evans suggests, as an explanation for his failure to find asymptomatic cases, that infectious

mononucleosis is now, under most circumstances, an infection of low contagiousness, tending to occur sporadically. Hoagland[37] was impressed with the absence of cases of infectious mononucleosis among the roommates of patients suffering from it at the U. S. Military Academy, where a group of young men is closely associated throughout a period of several years. With this as a starting point, Hoagland examined, with obvious skepticism, the evidence for the occurrence of epidemics of the disease. He excluded all reports of epidemics published before the report of the diagnostic value of the heterophil antibody test by Paul and Bunnell in 1932, a rather stern measure but one which seems justified in such an analysis. He also insisted upon other rigid criteria for diagnosis, including absorption tests for Forssman antibody. Although this study throws some shadow of doubt on most of the epidemics described since 1932, the reports of such epidemics cannot be dismissed, and Hoagland does not attempt to do so. It would appear desirable in the future, however, to examine the evidence for their existence more critically.

REPORTS OF ATTEMPTED VIRUS ISOLATION. Although infectious mononucleosis is generally regarded as an acute infection caused by a virus, the fact is not established, and the evidence for its experimental transmission to man or laboratory animals is meager. Of the laboratory animals which have been used in an attempt to recover a virus, only monkeys have yielded anything suggestive of positive results. To summarize these results briefly, it can be said that monkeys inoculated with blood from human cases of infectious mononucleosis have occasionally developed varying degrees and combinations of the following: fever, lymph node enlargement, mononuclear leukocytosis, or heterophil agglutinins in their sera[6,7,61]. Similar changes occurred in many of the monkeys inoculated by Wising[67] with bacteria-free suspensions of lymph nodes from patients in the acute stage of infectious mononucleosis, and in one instance it appeared that he was successful in transmitting an agent capable of producing these changes through five passages in monkeys. On the other hand, other investigators have obtained completely negative results following inoculation of monkeys with various materials, including blood and lymph node suspensions, from patients with the disease[27,41].

The attempts to produce infectious mononucleosis in human volunteers have yielded similarly doubtful results. There seems to be little doubt that of the 5 persons inoculated by Wising[67] with blood from patients with infectious mononucleosis, one developed typical signs and symptoms of the disease. However, in dealing with such a commonly encountered disorder, it would obviously be desirable to obtain positive results in more than one case before concluding that the disease was the result of the inoculation. Wising's studies also included inoculation of lymph node suspensions into 6 volunteers, none of whom developed any signs of illness. This negative result is particularly interesting in view of the fact that 5 of the volunteers received suspensions of the same lymph nodes which were thought to have produced the disease in monkeys. The studies of Evans[22] in 16 human volunteers, with the use of throat washings, fecal suspensions, and blood, gave results slightly suggestive of transmission of the disease in 3 cases. However, none of the 3 persons developed the full picture of infectious mononucleosis, and he concluded that the evidence for transmission of the disease to human

volunteers must be regarded as equivocal.

Listeria Monocytogenes as a Possible Cause of the Disease. The relationship of this organism to infectious mononucleosis is still a matter for debate. The subject was reviewed in detail in 1951 by Girard and Murray[33]. In brief, the evidence for a causal connection with infectious mononucleosis is its occasional isolation from the blood or cerebrospinal fluid of patients with the disease and the fact that animals infected with this organism show an increase in mononuclear cells in their blood. However, they do not develop heterophil agglutinins. Studies of agglutinins for *Listeria* in the sera of patients with infectious mononucleosis do not give much support to the concept of a causal relationship[39]. Girard and Murray believe that some cases of the disease may be caused by *Listeria monocytogenes* and that other cases may have a different etiology.

Infectious Mononucleosis as a Possible Disease of Hypersensitivity. EVIDENCE FAVORING THE CONCEPT. The idea that infectious mononucleosis represents an allergic process is not new and does not rest on any positive evidence. Nevertheless, the concept is an appealing one and might explain many of the obscure features of the disease. It derives chiefly from the clinical resemblance of infectious mononucleosis to the anaphylactic type of hypersensitivity following the administration of serum and certain drugs. This clinical picture is described in Longcope's excellent article[48]. As has been mentioned previously, the clinical picture of fever, a general enlargement of lymph nodes and sometimes of the spleen, rashes of a variety of sorts, and a generally benign course resembles that of serum or drug sickness.

The varied involvement of the nervous system in serum sickness is well described by Miller and Stanton[51] and bears a great resemblance to the neurologic disorders in infectious mononucleosis. For example, they list, among the neurologic complications of serum administration, radiculitis, polyneuritis and the Guillain-Barré syndrome, and cerebral and meningeal types, including optic neuritis. They believe that the common factor in such diverse effects is hypersensitivity of the anaphylactic type. Librach[46], in discussing a case of infectious mononucleosis with cerebral complications, suggests that involvement of the nervous system in this disease may have an allergic basis, pointing out that no known viral infection, with the possible exception of poliomyelitis, causes such widespread and bizarre evidences of involvement of the nervous system. Bernstein and Wolff[9] deprecate the theory that the neurologic complications have such a basis by pointing out that they may occur in almost any stage of the disease, rather than having a definite temporal relation to its onset.

The several serologic abnormalities in infectious mononucleosis suggest a nonspecific production of antibodies by a disease affecting the reticuloendothelial system. There is one obvious and important difficulty, however, in accepting the idea that they are nonspecific, namely that heterophil agglutinins appear to have high specificity for the disease. It is not established clearly, however, that they represent true antibodies.

EVIDENCE CONTRARY TO THE CONCEPT. One obvious objection to the theory of hypersensitivity as an important factor is encountered in the numerous reports of epidemics. It is easy to conceive of a moderately large group of patients reacting in an unusual fashion to an infection which ran a different clinical course in the much larger group from which they were drawn. As an

analogy, an outbreak of rheumatic fever during the course of widespread streptococcic infection in a large military post might be termed an epidemic of rheumatic fever if the nature of the disease were not understood to some extent. It would, however, be unreasonable to explain an outbreak of infectious mononucleosis with a very high incidence in any particular group on the basis of such a theory. It is because this aspect of the situation appears of such importance in evaluating the evidence for the presence or absence of hypersensitivity in the disease that mention has been made of reports which cast some doubt on the occurrence of epidemics. The matter seems to merit more careful study.

The lesions of infectious mononucleosis described earlier are certainly not those of the acute vasculitis which apparently is the basic lesion in serum and drug sickness. Moreover, the lesions of infectious mononucleosis, at least in the case of those in the lymph nodes, are said to be almost specific[31]. Finally, although the atypical lymphocytes of this disease are said to occur in other disorders, including allergic diseases, and might reflect only the marked lymphoid hyperplasia, their presence in large numbers is almost diagnostic of infectious mononucleosis.

THE POSSIBILITY OF HYPERSENSITIVITY TO BACTERIAL INFECTION AS AN ETIOLOGIC FACTOR. The fact that sore throat is such a frequent and early feature of infectious mononucleosis suggests that the disease begins as a pharyngitis. Joyce[10] lists the reported incidence of sore throat in various series of cases which have been reported, stressing its frequency. Further support for such a concept is provided by the frequency with which the cervical lymph nodes are enlarged. They tend to be the first nodes to enlarge, and are sometimes the only ones. The appearance of the pharynx is frequently suggestive of acute bacterial infection, with tonsillitis or diffuse redness and edema.

In the early stages of the study of the disease, many of the German clinicians believed that the hemolytic streptococcus was the causative agent, basing this opinion upon the frequent presence of this organism in the throat and the occasional occurrence of scarlatiniform rashes and nephritis during the course of the illness. Their views, as summarized by Tidy[63], were that the clinical picture of infectious mononucleosis was the result of "a constitutional lymphatic tendency in the individual which was called into activity by the angina", and that an identical angina in other persons would result in the common clinical picture with associated increase in neutrophilic granulocytes in the blood. This theory would probably be presented today as a hypersensitivity reaction to bacterial infection. It has, apparently, been abandoned as an explanation for the pathogenesis of infectious mononucleosis, but it might well be given new consideration.

A major reason for this suggestion is the great frequency with which pathogenic bacteria can be cultured from the throats of patients with infectious mononucleosis. The beta-hemolytic streptococcus is of particular interest in this connection. The incidence of its presence in throat cultures in the disease is difficult to assess, since in many of the published reports the methods used for isolation and identification of the organism are not given in detail. As a generalization, it can be said that the beta-hemolytic streptococcus has been reported frequently in throat cultures in many articles describing the clinical picture of infectious mononucleosis. As an example, in Wechsler's[65] large series of cases, the incidence was 41%.

It seems reasonably certain that the hemolytic streptococcus is not always found, even when it is looked for with care. However, other pathogenic bacteria may be present. Campbell[12] has been impressed with the incidence of coagulase-positive staphylococci in the throats of patients with infectious mononucleosis, as compared with a large control group consisting of various kinds of pharyngitis. Although he does not attach much significance to the finding, his tables also reveal the presence of beta-hemolytic streptococci in cultures of the throat in 24 of the 52 cases of infectious mononucleosis studied.

Other organisms, such as the pneumococcus and *Hemophilus influenzae*, have been reported in throat cultures in the disease. Vincent's organisms are often demonstrable, particularly in cases accompanied by stomatitis.

Two small pieces of clinical evidence to suggest that bacterial infection may initiate the disease will be mentioned, for their general interest and possible bearing on the thesis, but without any attempt to draw important conclusions from them. One of them is that, in rare instances, infectious mononucleosis begins with the typical picture of acute tonsillitis[8]. The other is a personal observation of a case of infectious mononucleosis in a young woman, followed within a week by follicular tonsillitis in the 2 older members of her family. Beta-hemolytic streptococci were cultured from the throats of all 3 of these patients, and it is tempting to speculate that the younger person reacted in an unusual way to infection with the same organism that caused the usual picture of bacterial infection in her elders.

It is generally considered that infectious mononucleosis is a specific infection caused by a virus, and that the occurrence of pathogenic bacteria in the throat represents secondary bacterial infection. There is little doubt that pharyngitis is an early and prominent feature of certain viral infections, such as measles, but it is rarely as severe as that encountered in some cases of infectious mononucleosis. The high incidence of pathogenic bacteria in the pharynx in infectious mononucleosis is impressive, and the conclusion that these bacteria have infected the pharynx following viral infection does not seem justified without more critical study. Throat cultures certainly should be done in the early stages of the disease, even in instances where the throat does not look inflamed.

An obvious objection to the concept of bacterial hypersensitivity, on the basis of evidence now available, is that it would require acceptance of the idea that the clinical picture of infectious mononucleosis could result from infection caused by more than one type of bacteria. Again, it would be helpful to have more extensive and detailed information on bacteriologic studies to evaluate this point.

In regard to the possibility that the beta-hemolytic streptococcus may play a causal role, at least in some patients, anti-streptolysin titers during the course of the disease should be of interest. In a few reported instances they have been studied and found to be elevated[5,44]. However, it is difficult to draw any conclusions from these reports, since, as a rule, they were done on patients demonstrated to have the organism in their throats and the increased titers might be explained by bacterial infection alone.

THE EFFECT OF CORTISONE AND ACTH IN INFECTIOUS MONONUCLEOSIS. There are only a few published reports on the use of cortisone and ACTH in infectious mononucleosis, and certainly these hormones are not indicated in the treatment of the relatively mild illness

presented by most patients with the disease. Two of the case reports might be mentioned as of especial interest. Doran and Weisberger[18] describe striking clinical improvement in a patient severely ill with infectious mononucleosis. Fiese *et al.*[29] report similar improvement in a patient with the Guillain-Barré syndrome thought to be associated with the disease; the diagnosis in this case rested entirely on the presence of heterophil agglutinins. Obviously these cases do not constitute any strong evidence for the role of hypersensitivity in infectious mononucleosis, since cortisone and ACTH may have striking effects in a variety of inflammatory processes.

Conclusions. The etiology of infectious mononucleosis is still not established. Although it is generally regarded as a specific viral infection, there is no convincing evidence that this is the case. Many of the clinical and laboratory features suggest that it may be a disease of hypersensitivity, but this concept of its pathogenesis does not rest upon positive evidence. The reported occurrence of epidemics of the disease is evidence against such a concept. The possible role of an allergic reaction to bacterial infection deserves more attention.

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NEUROLOGY AND PSYCHIATRY

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THE DRUG THERAPY OF PARKINSON'S SYNDROME: A REVIEW

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ALTHOUGH toxic, neoplastic and traumatic disturbances in certain portions of the extrapyramidal system may occasionally produce the clinical picture of Parkinsonism, the vast majority of cases of this disease which the physician is called upon to treat fall into one of the three following varieties: 1) idiopathic, 2) postencephalitic, 3) arteriosclerotic[54]. Idiopathic Parkinsonism (also often referred to in the literature as "paralysis agitans" or "essential Parkinsonism") is a chronic progressive degenerative disease with onset of symptomatology usually, but not always, in late middle life. This variety is generally diagnosed when there is neither a known history of fever or lethargy preceding the onset of tremor and rigidity nor the clinical or pathological findings of atherosclerosis[21]. The diagnosis of arteriosclerotic Parkinsonism can usually be made more readily than that of the other two major types because of the well-known clinical and pathological evidences of associated atherosclerosis of the central nervous system or other systems. Postencephalitic Parkinsonism[54,57] may occur from a few months to several decades after an attack of acute encephalitis. This variety of Parkinsonism may be seen in the third, fourth, and fifth decades of life, (or later) and is especially likely to be associated with ocular symptoms (oculogyric crises, defective pupillary contraction, weakness of convergence, fluttering of the eyelids), autonomic dysfunction (greasy skin, excessive salivation) and emotional or behavioral disturbances.

One of the greatest draw-backs to the scientific evaluation of any type of treatment of Parkinson's syndrome is the fact that the various investigators disagree on the proper method of measuring "improvement". Some observers believe that the only reliable test of improvement is the "subjective" evaluation of the patient himself[14]. Others base their opinions on such "objective" findings as are revealed by visible "improvement in walking and turning, combing the hair, shaving, washing, talking and performing household chores", and the like, as well as supporting statements from relatives, friends and other physicians[4,40,66,68]. It has been found difficult, if not impossible, to devise tests which are both practical and sufficiently objective to permit accurate and reliable measure-

ment of the amount of improvement of spasticity and tremor. Many investigators who rely on "objective" evidences of improvement also lay great stress on the results of repeated neurological examinations, electromyographic recordings and various tests of psychomotor dexterity[14,34,48,53,58]. It is quite common for patients to express great enthusiasm over subjectively perceived improvement in spite of a total absence of confirmatory objective evidence[5,16]. There is good reason to believe that no known regimen of treatment results in more than 25 to 35% improvement[2,55,66,68].

Another factor which complicates exact evaluation of the amount or degree of improvement in Parkinson's syndrome is the well-known fact that emotional stress alone is capable of markedly increasing a Parkinsonian tremor[1,52,54]. Under hypnosis the tremor in some patients can be diminished or even abolished altogether[10]. Even "short stresses"[67] such as "door slams, criticisms, interviews, missing trains, and the host of minor burdens met with in ordinary life" increase tremor "by producing annoyance, irritation, fear, anxiety, tension and anger." The increase in symptoms is temporary and varies from individual to individual. Most patients feel better, are less rigid, and have less tremor as their environment is enriched by quiet, comfort, security, and contentment. Denny-Brown goes so far as to say that any sudden change in the course of Parkinson's disease is invariably related to such factors as emotional trauma, injury, infections and other upsetting situations of moderate duration. Such stresses are those lasting hours to days, for example, periods of overwork, an infected tooth, a minor fall with a little bruising, a cold or a gastric upset, the visit of an unwelcome guest, a spell of extreme weather or the absence of a loved one or a person on whom great dependence has been placed. They also include stresses of long duration which persist for weeks, months and years, for example, the death of loved ones, operations and illnesses that are protracted, loss of large amounts of property, and so forth"[67].

The possible role that personality structure plays in the etiology and response to therapy of Parkinson's syndrome has been studied for many years. Jelliffe[45] used the psychoanalytic approach and concluded that brain lesions were of less importance than the personality in the pathogenesis of paralysis agitans. Booth[6,7] and Hendrick[43] shared the same general opinion. Benda and Cobb[3] postulated that "it may be that persons with marked motor drive are more likely to develop the syndrome than those of a more sedentary life." Yaskin's opinion[79] that premorbid personality traits emerge in an intensified form "as a result of the disease" sounds logical and convincing.

Observations such as the following should certainly be encouraged, but, at least for the present, they shed only questionable light on this subject: "Gotthard Booth . . . concluded that these patients are dominated by needs for individuality, action and self-assertion towards the influences of the environment. . . whereas on a structured test such as the Wechsler-Bellevue these subjects produce a good range of concrete ideas, on the unstructured Rorschach they show an impoverishment of abstract imagination, or in other words, they are confined to the obvious and the stereotyped[13]." Markovich and Schwab[52] studied a mixed (from the etiological standpoint) group of 65 cases of Parkinson's syndrome for 3 to 5 years and came to the following interesting conclusions: Regardless of the therapy used, "62% of those patients who were subject to depressions, ex-

tensive worriers, chronic complainers, patients with extensive drive and ambition who were subject to mood swings, and who would . . . be regarded as difficult personalities or neurotic people . . . showed progression of their symptoms, whereas only 25% of those with stable deviations of personality structure showed a similar progression." An earlier article[67] describes the situation even more clearly: "The normal, easy-going, placid person usually responds favorably to medical treatment. The dependent, passive, suggestible patient also does well. The tense, driving, restless, ambitious personality is most difficult to help. Reluctant to accept his disability, he strives constantly to seek a complete cure. The unavoidable reduction in activity and the need of a longer time scale is incompatible with his way of life. The depressing effect of the antispasmodic drugs irritates rather than soothes. This group of people is always dissatisfied and critical of medical failure to counteract the symptoms in an efficient and complete manner. Patients with psychopathic states, depressions and paranoid states react even more unsatisfactorily to medical help. In this disease all the usual means of expression are seriously modified. The facies is rigid; gesticulation can only be carried out with difficulty and without spontaneity; body posture is fixed; even speech becomes slowed . . . and later unintelligible or even impossible. It is understandable that the inability to give vent to feelings in the ordinary way must be a chronic and bitter source of frustration and irritation."

There are other complications to any form of drug treatment of Parkinsonism. For example[39], a new remedy is likely to achieve good results at first but such benefit may not persist. This should not be surprising as it is common to find few or no striking objective changes in patients who claim marked improvement from medicinal treatment. Suggestion is undoubtedly a large factor with many patients. The optimism caused by early improvement is often replaced by dejection, following a relapse, which is reflected in an attitude of hostility and resentment toward the doctor. Some patients[28] are so desperate for a cure that they readily tire of any remedy and demand new ones in rapid succession. Others are highly distrustful of new drugs for fear of being made subjects of experiment. Another uncontrollable variable is the fact that in Parkinsonism the patient rather than the physician determines the therapy, because the length of the illness leads patients to shift and experiment with various drugs until they find those that provide the greatest comfort and relief from symptoms. However, those drugs which possess some positive value to the patient usually find their true level of use in accordance with their merits.

The Commonly Accepted Drugs. A. SYNTHETIC ANTISPASMODICS. 1. *Artane (Trihexyphenidyl).* This antispasmodic is a product of the Lederle research organization and, chemically, is 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride. Compared with atropine, Artane has one-half as strong an antispasmodic action, one-eighth as much antisialogogue potency, and one-tenth as much cardiovagal inhibitory effect[18,24]. It is supplied in scored 2-mg. and 5-mg. tablets, as well as in elixir form, with each fluid dram (4 cc.) containing 2 mg. of the drug. Artane should be given orally, 3 or 4 times a day. The initial dose should be small, with subsequent gradual increases over a period of 4 to 6 days or more, until the effective level is reached. The drug is usually well tolerated under this regimen[24,25]. When started as initial therapy, 1 mg. of Artane should be

given the first day, and 2 mg. the second day, with further increases of 2 mg. each day until a total of 6 to 10 mg. are given daily. Many patients derive maximum benefit from this total dose of 6 to 10 mg. Nausea may be alleviated by the administration of Artane with or after meals. Benzedrine or Dexedrine may be added on arising, and repeated at 11:00 a.m. if early morning psychic depression exists[17]. Postencephalitic patients nearly always require a larger dose of Artane than either the arteriosclerotic or the idiopathic types[11,24,28,72]. Those with excessive salivation will prefer their Artane after meals, and may require, in addition, small amounts of atropine[54,72]. It is the opinion of some observers that Artane should nearly always, or at least often, be used in combination with the solanaceous agents such as hyoscine (scopolamine) hydrobromide, tincture of belladonna or tincture of hyoscyamus, Rabellon, or Vinobel[17,74]. Side reactions to Artane are unusual but have included dry mouth, nausea, vomiting, dizziness, sore mouth, blurring of vision, headache, nervousness, tinnitus, generalized pruritus, mental confusion, memory impairment, excitement, spider angiomas, and visual and auditory hallucinations[17,36,44,68,79]. Severe reactions are observed mainly after protracted treatment with unnecessarily large doses[73]. When used in total daily doses of 10 mg. or less, Artane is rarely accompanied by disturbing side effects, and is notably free of toxic effects on the cardiac vagus, blood pressure and circulation[16,24,68]. The effect of Artane on tremor is questionable[11,24,63], but it is especially effective in reducing the muscle spasm of many cases of Parkinsonism[73]. It usually tends to relieve the depression and mental inertia characteristic of this syndrome[24]. If tremor is pronounced, especially in arteriosclerotic cases, one can supplement the drug with small amounts of scopolamine[24]. Artane is a particularly valuable adjunct in the treatment of arteriosclerotic Parkinsonism because, in contrast to atropine, it is believed that it will not precipitate glaucoma[24]. Many observers are of the opinion that Artane is the drug of choice, at least for the arteriosclerotic and idiopathic types[16,24,25,31,42,48,63]. Artane has been studied in more clinical research projects in the last 5 years than any other anti-Parkinsonian agent.

The very recent report by Doshay, Constable, and Zier[29] on the 5-year follow-up of 411 patients treated with Artane is especially entitled to some brief quotations: "Artane is commonly accepted as the standby in the treatment of all forms of paralysis agitans. . . . The mean of the current ages of the patients was 41 to 45 in the postencephalitic group, 51 to 55 in the idiopathic group, and 61 to 65 in the arteriosclerotic group. The dose of Artane varied from 2 to 7.5 mg. per day in arteriosclerotic cases, 6 to 10 mg. per day in idiopathic cases, and 7.5 to 30 mg. per day in postencephalitic cases. Seventy-three per cent of the patients showed improvement while on Artane. In all groups of paralysis agitans the drug is about as effective against tremor as it is against rigidity (51% and 53%). . . . Artane was used alone in from 50 to 70% of the patients except that another drug was added from time to time in efforts to combat one or another symptom. . . . Artane was combined with scopolamine (Hyoscine) in 98 cases and with Benadryl in 105 cases to help counteract rigidity; with Benzedrine or Dexedrine in 44 cases to combat lethargy and akinesia; with MK-02 in 100 cases to counteract cramps, spasms, contractures, and deformity."

2. *Pipanol Hydrochloride* (the Winthrop-Stearns brand of Trihexyphen-

idyl hydrochloride) is 1-cyclohexyl-1-phenyl-1-hydroxy-3-piper-idinopropane hydrochloride[54,71]. It seems to be identical with Artane in effectiveness against the clinical manifestations of Parkinson's syndrome, in dosage and in side effects. It is supplied in scored white tablets of 2-mg. and 5-mg. sizes, as well as in elixir form, with each fluid dram (4 cc.) containing 2 mg. of the drug.

3. *Pagitane Hydrochloride* (Cycrimine Hydrochloride, Lilly). Chemically this drug is a derivative of aminopropanol. Its chemical formula is 1-phenyl-1-cyclopentyl-3-piperidino-1-propanol hydrochloride. Its chemical similarity to Artane and Pipanol Hydrochloride is obvious. Pagitane Hydrochloride is a new potent antispasmodic drug which at times is described in the literature under the name of "Antispasmodic Compound 08958[50,51,55]". It is supplied in 1.25-mg. orange sugar-coated tablets, as well as in 2.5-mg. brown sugar-coated tablets. Preliminary investigation with this new antispasmodic suggests that its general effectiveness is approximately the same as that of Artane and Pipanol Hydrochloride, but that it is more effective in the treatment of postencephalitic Parkinsonism[50]. It reduces rigidity fairly regularly and often diminishes tremor. It has controlled oculogyric crises when all other drugs have failed[50,55]. The following are the initial dosages recommended: Postencephalitic, 2.5 mg. t.i.d., idiopathic and arteriosclerotic, 1.25 mg. t.i.d., with a gradual build up to tolerance over a 7- to 10-day period. In most patients with idiopathic and arteriosclerotic Parkinsonism dosages between 7.5 to 15 mg. are therapeutically effective and not associated with toxic symptoms[13]. The postencephalitic type often tolerate and experience marked symptomatic relief of symptoms with dosages as high as 30 mg. daily[50,55]. Doshay and Zier[27] state that, "Old patients can be maintained comfortably on 1.25 mg. three times a day. The younger patients tolerate 5 mg. three times daily without difficulty." Significant side effects are dry mouth, dizziness or lightheadedness, "feeling of stupidity," gastrointestinal disturbances, nausea and vomiting, anorexia, epigastric discomfort, blurred vision, hallucinations, disorientation, sore mouth and tongue, weakness, palpitation, insomnia, salty taste, and numbness[50,51,55]. Pagitane Hydrochloride has been considered by some to be more potent than Artane, both in beneficial effects and in side reactions[50,51]. Arteriosclerotic patients tolerate Pagitane Hydrochloride the least well of the three types, at times developing psychotic reactions with hallucinations and disorientation, which, however, subside in a day or two following discontinuance of the medication. Hence, a slow build-up of the daily dosage of Pagitane Hydrochloride, over a period of 10 days or more is indicated in arteriosclerotic Parkinsonism. Pagitane Hydrochloride should not be administered to patients suffering from glaucoma, tachycardia or urinary retention.

4. *Parsidol* (identified as W483 during clinical trials in the United States; as R.P. 3356 and Parsidol in France, and in Great Britain as Lysivane and Ethopropazine). It is the hydrochloride of diethylaminopropyl phenothiazine. Parsidol is produced by the Warner-Chilcott Laboratories and is available in scored 10-mg. and 50-mg. tablets. The main benefit of Parsidol is the reduction of muscular rigidity, but it also seems to reduce tremor at times[40,54,59,61]. When initiating therapy, the starting dose should be 10 mg. four times daily. This may be increased gradually to 150 or 200 mg. per day over a period of about 14 days, for mild or moderately severe cases. Severe

cases may require a further gradual increase to 500 or 600 mg. per day. Side effects[39,40,54,63,70] include drowsiness, dryness of the mouth, nausea, vomiting, tinnitus, depression, palpitation, vertigo, difficulty in visual accommodation, tingling of skin, cramps in the limbs, tiredness and "heaviness", lassitude and ataxia. Toxic effects appear to be more common and more severe than with Artane[1] and can be quite disturbing to older patients[27]. Parsidol should not be prescribed for patients with glaucoma. Some investigators are convinced that Parsidol is the drug of choice for the treatment of all new cases of Parkinsonism, regardless of etiology[40]. Others believe that its effectiveness is about the same as that of hyoscine, or that it is a good adjunct when combined with such drugs as hyoscine[63]. In general, it is most effective when combined with one or more other drugs such as Artane, Benadryl, or hyoscine. Some find it inferior to Artane[63].

5. *Panparnit* (Caramiphen, Parpanit). This is a synthetic drug with the structural formula of 2-diethylaminoethyl-1-phenyl-cyclopentane carboxylate hydrochloride. It is manufactured by Geigy Pharmaceuticals and is available in red tablets of 12.5-mg. and orange tablets of 50-mg. size. There is a wide range of individual variation in tolerance for Panparnit, but it is safe to begin with an initial dosage of 12.5 mg. three times daily, immediately after meals. These dosages are gradually increased to tolerance over a period of a week until about 50 mg. are given five times daily. Those doses which are not administered immediately after meals should be given with a full glass of water. The main effect of Panparnit is the reduction of rigidity. It is less effective against tremor than the belladonna compounds[66], but even in this respect there is dissenting opinion[47]. Some observers reported that Panparnit is superior to hyoscine[48]. Others failed to observe any striking difference in therapeutic effectiveness between Panparnit and the various solanaceous alkaloids which have been in use for many years[33,63,69]. Panparnit is said to be more toxic in older patients than Artane but more effective in reducing tremor[66]. There is some evidence that this drug should not be used at all in Parkinsonism because of the very high incidence of less serious toxic side effects[54] in both arteriosclerotic and idiopathic types, "but that it can be used as substitution therapy in postencephalitic cases"[25], or merely "limited to younger patients" altogether[27]. It is less effective in general than Artane[16,37]. Some patients respond well to a combination of Artane and Panparnit[66,68] or to Benadryl and Panparnit[66]. Toxic symptoms[25,39,66,69] include dizziness, palpitation, tinnitus, giddiness, anorexia, nausea, vomiting, epigastric burning, weakness or "light" feelings in the legs, floating feelings, headache, excessive perspiration, dry mouth, drowsiness, blurring of vision, and diplopia. In one series of cases[24] Panparnit caused dryness of the mouth and blurred vision only one-fourth as often as Artane, but caused other disturbing side effects ten times as often as Artane.

6. *Cogentin* (MK-02, Benztropine Sulfonate). This new synthetic compound has the structural formula, tropine benzohydryl ether methane sulfonate. It combines the active radicles of atropine and Benadryl. Although this drug has only been available to clinical investigators[26,27,28,30,34,58,74] recently, it will very shortly be marketed by the Sharp & Dohme Division of Merck & Company, Inc. It has already received Food and Drug Administration acceptance, and will probably be made available in 2-mg. white double-scored

tablets. It has a powerful antispasmodic action, works peripherally, and seems devoid of cerebral stimulating qualities. The drug has a cumulative action that permits treatment twice a day or sometimes even once a day to be effective. It is practically nontoxic and is recommended particularly for the control of rigidity, sialorrhea, spasm, fixed facies in postencephalitic patients and for severe tremors in arteriosclerotic patients. The average daily effective dose is between 0.5 mg. and 5 mg. Initial dosages should be approximately as follows: Postencephalitic cases, 0.5 mg. three times daily; idiopathic and arteriosclerotic cases, 0.5 mg. once or twice daily. Maximum effective dosages can then be gradually reached in about 10 days. Postencephalitic patients, with their usual high tolerance for anti-Parkinsonian drugs, can usually tolerate 2 to 5 mg. or more of Cogentin daily. Idiopathic and arteriosclerotic patients will usually require from 0.5 to 2.0 mg. daily. The chief side reaction of Cogentin is dryness of the mouth, and hence patients are advised to take the compound after meals. Often, Cogentin alone is insufficient as patients "on" it alone tend to become listless and somewhat depressed. Hence it is well to combine it with Artane, which is a cerebral stimulant. For patients already on Artane it is well not to start reducing the Artane until Cogentin has been added for at least a week. Then, over a period of a month or so, the proper combination of cogentin and Artane can be determined When they are used together it is preferable to administer Artane before meals and Cogentin after meals. Movement is said to be rendered easier with Cogentin and Artane therapy than when Artane is combined with Bellabulgara, hyoscine, stramonium, and others. Cogentin often obliterates almost completely the typical Parkinsonian facies, and tends to relieve muscle cramps. Cogentin likewise may control sialorrhea better than atropine and usually without the distress of a parched throat, difficulty in swallowing and loss of appetite. Cogentin has the ability to control severe tremor, a factor of great benefit to older patients in particular. Any side reactions that may occur, such as dryness of the throat, weakness or lassitude are either transient in nature or disappear within a day or two after cessation of treatment. Cogentin is equally well tolerated in all three major types of the Parkinsonian syndrome, and has no deleterious effects on the pulse, blood pressure, cardiac branch of the vagus or the gastrointestinal system.

POTATO PLANT PRODUCTS. 7. *Hyoscine (Scopolamine).* This is an extract of the solanaceous plants, especially stramonium, and is available in 1/200 grain (0.3 mg.), 1/150 grain (0.45 mg.) and 1/100 grain (0.6 mg.) tablets. Older patients should be started on one 1/200 grain dose daily, after breakfast. Every third or fourth day this daily dose may be increased by 1/200 grain until the total daily dose is 1/200 grain tablet two to four times daily. Younger patients should be started on 1/150 or 1/100 of a grain doses daily, and gradually have this dose increased to as high as 1/50 grain three or four times daily. Some clinicians report that Artane and Panparnit are superior to hyoscine[48]. One observer[63] asserted that "hyoscine is the drug of choice . . . in the younger cases of postencephalitic" Parkinsonism "partly because they were able to tolerate larger doses of the drug, and partly because they were more disabled by rigidity, reduction of which appeared to be the main therapeutic effect of the drug." There is a disagreement in the literature as to the effects of hyoscine on tremor. For example, Miller[54] states that "Hyoscine

has no appreciable effect on tremor," but Doshay and Zier[27] report that "hyoscine is our very best current drug for the control of tremor." Hyoscine causes dryness of the mouth and blurred vision only slightly more often than Artane, but causes almost three times as many other disturbing side reactions (such as dizziness, tachycardia, prostration, nausea and depression) as Artane[24]. Side reactions which pass unnoticed in young patients may prove very disturbing to elderly arteriosclerotic patients, who are sensitive to all types of medication.

8. *Stramonium.* This is best administered in the form of the tincture of stramonium[23,27,43,77]. Stramonium has a greater content of hyoscine than other potato plants. Hence it is especially effective for the control of tremor, tension and excitement, although it has some effect on rigidity as well. It is easily tolerated by older patients. When using the tincture it is well to begin with 5 drops in water after each meal and gradually increase the daily dose by increasing each of the *post cibum* doses daily by 2 drops until tolerance is reached. The total final daily dosage should never exceed ten times the initial day's total dosage. An occasional investigator believes that Artane has not been demonstrated to be superior to stramonium. "Artane was slightly superior in objective tests of upper extremity dexterity, strength, and mental alertness. Stramonium was superior to Artane in objective tests of lower extremity dexterity, and walking[4]. Denny-Brown[12] stated that "recent studies indicate that Artane is almost as efficacious as stramonium or hyoscine and possibly induces fewer unpleasant side effects."

9. *Atropine.* This drug, in the form of a 0.5% solution of atropine sulfate, is best administered in 3 drop doses, orally, with an interval of at least six hours between dosages because of the slowness of excretion of the drug. The dose should be increased 1 drop three times a day every three days, until about 10 drops three times daily are reached. It is rarely necessary to go beyond this maximum dosage except for the control of oculogyric crises, in which case the dose may be elevated to 15 drops three times daily. Atropine is an effective drug for the relaxation of spasm and rigidity[27]. Although some dryness of the mouth and blurring of vision is observed in most patients successfully treated with atropine, most patients can tolerate a moderate amount of these two symptoms if they are not accompanied by more disturbing types of reaction. Atropine in 0.5% solution has special value and is well tolerated in postencephalitic Parkinsonism, especially among the younger and earlier cases. It may be used in small amounts in idiopathic cases, but never in arteriosclerotic Parkinsonism because of the hazard of glaucoma and circulatory disturbances[24,25]. Massive doses of atropine sulfate may result in excitement and hallucinations. Prolonged treatment, even with smaller doses, may result in severe or even fatal disturbances of tonus, motility and secretion of the gastrointestinal tract. Postmortem examination of 6 cases revealed the formation of megasigmoid or megacolon, with ulceration or ileus and acute dilatation of the stomach[24,75]. Toxic reactions also include occasional nausea, vomiting, tachycardia and dizziness[27].

10. *Bellabulgara.* This is a root extract of Bulgarian belladonna. It is manufactured by Lederle Laboratories in one unit, chocolate colored tablets, containing 0.45 mg. of the alkaloids, atropine and hyoscyamine, as well as a trace of hyoscine. Bellabulgara is started initially by administering one-half of a tablet after each meal. Then,

one *post cibum* dose daily is increased by one-half of a tablet until the optimum dose is reached. Neal[22,56] believes that Bellabulgara is the most effective treatment for postencephalitic Parkinsonism, as the toxic symptoms are less disturbing and the patients' tolerance seemed higher. The three belladonna preparations, Bellabulgara, Vinobel, and Rabellon, have about equal composition and similar effects in idiopathic and postencephalitic cases. All three should be administered in smaller doses in arteriosclerotic cases.

11. *Vinobel.* This is a root extract of domestic potato plants that is manufactured by William S. Merrell Company. It is available in two forms: a brown tablet containing 0.4 mg. of the active alkaloids and a pink tablet containing 0.8 mg. of the same. It is a good antispasmodic. The larger tablet should be used for younger patients and the smaller for older patients[23,27,62]. In treating postencephalitic patients it is well to start with an 0.4 mg. dose, and then increase it slowly to the level of tolerance. The average optimal dose is about seven to ten 0.4 mg. tablets daily. The symptoms most improved are rigidity, salivation, postural disturbances and oculogyric crises[22]. In one large series of cases[72] of postencephalitic Parkinsonism treated with Vinobel, over 99% of cases of moderate severity and over 83% of cases of marked severity were improved.

12. *Rabellon.* This is a synthetic compound made from drugs extracted from the American belladonna root. It is manufactured by Sharp & Dohme Laboratories. It comes in the form of a double-scored white tablet. Each tablet contains 0.4507 mg. of hyoscyamine hydrobromide, 0.0372 mg. of atropine sulfate, and 0.0119 mg. of scopolamine hydrobromide. Rabellon is started with one-fourth of a tablet three times daily, and is increased one-fourth of a tablet three times daily until about three to nine tablets are taken daily, depending upon the tolerance of the individual patient. It is a good muscle relaxant but has little if any effect against tremor. Rabellon may be combined with other anti-Parkinsonian drugs such as Artane and Benadryl[34]. The synthetic preparations such as Rabellon are just as effective as the natural extracts of belladonna roots, if the syntheses are in the right proportion and the drugs are given in the proper dosages.

SYNTHETIC ANTIHISTAMINES. 13. *Benadryl (Diphenhydramine).* The structural formula of this synthetic antihistamine is B-dimethylaminoethyl benzohydryl ether hydrocholoride. It is manufactured by Parke, Davis & Company in 25-mg. red and white capsules and 50-mg. red capsules[27,34]. It is generally employed in 50-mg. doses two to four times daily. It has occasionally[16] seemed to be the drug of choice in early cases of Parkinson's syndrome in which the symptoms are of a minor nature and the patient does not wish to be bothered by the side reactions of the stronger antispasmodics. The initial dose of the drug[53] should be given at a time when the patients will not be called upon to perform skilled movements depending upon acts of judgment, as drowsiness or dizziness may occur in sensitive patients and thereby endanger their lives. In general Benadryl is now considered an adjuvant drug[51], to be used in combination with the belladonna drugs or the new synthetic compounds[5,9,25,36,63,65,68,79]. Its maximum therapeutic effect occurs within 10 days[64]. When used alone, complete relapse occurs within 48 hours after its withdrawal. The slight sedative effect of Benadryl is probably a factor in those cases of moderate or severe involvement which improve under its use[9,17]. Rigidity is frequently improved[63]. Tremor usually responds

poorly to Benadryl especially if it is at all severe[14,19,64]. The most common side effect encountered with Benadryl is drowsiness[79]. This can usually be offset by the judicious use of amphetamine (5 to 10 mg. once or twice daily) or by substituting Thephorin for Benadryl[63]. Other toxic reactions (which are usually of a mild non-incapacitating degree) are: Dryness of the mouth, dizziness, weakness and easy fatigability, incoordination, blurring of vision and gastrointestinal upsets[5,19,53,68,79].

14. *Thephorin (Phenindamine).* This antihistamine is 2-methyl-9-phenyl-tetrahydro-1-pyridindene hydrogen tartrate. It is marketed by Hoffman-La Roche, Inc. in 25-mg. yellow tablets. It is used extensively in the treatment of Parkinsonism but never at the same time as Benadryl. Thephorin should be used as an adjuvant drug to Artane or scopolamine[5,14,36,38] rather than alone[25,40]. If used alone, Thephorin is especially ineffective against arteriosclerotic or far advanced Parkinsonism of any type[14]. Thephorin is often substituted for Benadryl if drowsiness of an objectionable degree results from use of the latter drug. Although toxic side effects of Thephorin are relatively uncommon, the following have been reported: transient gastrointestinal upsets such as nausea and vomiting, tension, restlessness, insomnia, and rarely somnolence[5,36,79]. Schwab[65] summarized his experience with Thephorin as follows: "Thephorin, 25 mg. four times a day, with a maximum dose of 50 mg. four times a day, is most effective when combined with Artane. When this combination is given to patients in elixir form so that 2 mg. of Artane and 25 mg. of Thephorin are dissolved in each 4 cc. of the elixir or vehicle, a fairly palatable and extremely useful mixture is available."

Comments on Drug Therapy. 1. BELLADONNA ALKALOIDS. Any treatment with belladonna alkaloids seems to be unsatisfactory unless doses are given which produce definite side effects but avoid more serious toxic manifestations[75]. These drugs usually give the patient a feeling of increased activity and of lessening stiffness. Among the older clinicians it was almost universally accepted that the belladonna root extracts had very little beneficial effect in arteriosclerotic cases of Parkinsonism as compared to the postencephalitic[22]. The "normal" side effects of all the belladonna alkaloids are similar and include dry mouth and some blurred vision in practically every case effectively treated. Toxic symptoms include dysarthria, dysphagia, diplopia, diarrhea, constipation, urinary retention, dizziness, headache, mental confusion[62]. Whenever toxic symptoms appear, the dosage should be reduced to the level of two days prior to their onset. This reduced dosage should be maintained for at least one week before the medication is again increased. Contraindications to the use of these drugs are advanced arteriosclerotic disease of the heart or the peripheral vessels, chronic nephritis, glaucoma, malnutrition and dehydration. Belladonna alkaloids, in toxic doses particularly, undoubtedly tend to increase the incidence of hyperthermia in Parkinson's syndrome. It has been known for years that many patients with Parkinson's syndrome tolerate extremes of temperature poorly[20]. Several cases of severe heat reactions and death among patients treated with belladonna alkaloids during extremely hot weather are on record[49].

If a patient who has been taking maximal doses of one or more of the belladonna alkaloids suddenly omits his treatment it is essential that tolerance again be acquired slowly. Otherwise

serious toxic symptoms may make their appearance. Occasionally when a patient omits his treatment a "Parkinsonian crisis" or a severe oculogyric crisis is precipitated, and he becomes totally rigid and immobile. This rare but alarming state of affairs soon responds to the renewal of drug treatment[39,64].

2. RESPONSE TO DRUGS. By and large, the patients who respond best to drug therapy are those in an intermediate stage of the disease. Patients with early signs of Parkinsonism, who are only slightly inconvenienced, will often object more to the side reactions or inconveniences associated with their medication than they do to the symptoms of the disease. When patients are bedridden and helpless with far advanced Parkinsonism, the therapeutic benefits derived from the necessarily large doses of drugs are often overshadowed by the associated toxic side reactions. Those patients who are still ambulatory and yet considerably handicapped are most successfully treated with drugs[17,55].

There is no way of accurately predicting which drug will have the best therapeutic effect in the case of any individual patient. Trial and error still remain the only method of choice[40]. No single drug can be expected to be beneficial in every case. The most suitable treatment or combination of treatments must depend upon the therapeutic requirements of the individual patient. This is so because we are dealing with different age groups, types of Parkinsonism and tolerances in the patients. A drug that may prove a blessing to the postencephalitic patient may be harmful to the arteriosclerotic patient. One must always remember that older patients are extremely sensitive to almost any form of drug therapy[28].

3. GRADUAL INCREASE OR DECREASE IN DOSAGE. Regardless of what drug or drugs are used in the treatment of Parkinson's syndrome, the principle of gradually increasing dosages when initiating therapy should be followed. The time interval necessary for stabilization of dosage may vary from a week to several months, depending upon the patient's tolerance, age, number and type of drugs employed, type of disease, and personality structure[17,22,39,54,73]. Patients on one or more drugs should not be "switched" precipitously to a new drug, regardless of the supposed merits of the latter. The new drug should be added in small doses and gradually increased while the previous medication is gradually reduced and eventually discontinued.

4. TOXIC EFFECT OF DRUGS. In the majority of cases the patient eventually becomes accustomed to the effect of any anti-Parkinsonian drug and will derive little benefit from its use unless the dose is increased to an undesirable degree. Hence, a relatively frequent change of medicinal agents is usually indicated. Yaskin[79] believes that it is well to discontinue all medications at times, in order to "clear the system of drugs, even at the cost of increasing tremor and rigidity."

5. EFFECT OF ACTH. Corticotropin has been tried on cases of arteriosclerotic and postencephalitic Parkinsonism. There was no significant effect on the dyskinesia or on the course of the illness in any patient. The rigidity was not affected[41].

6. USE OF SEDATIVES. There is some difference of opinion in the literature in regard to the use of sedatives in Parkinson's syndrome. Blumberg and Dattner[5] state that "some drugs frequently have a definitely unfavourable effect on this disease. This is especially true of the barbiturates." Yaskin[79] agrees with this, and adds that "insomnia occurring in postencephalitic Parkinson's disease or complicating psy-

chotic reactions (toxic, structural, or constitutional) are often a major therapeutic problem. I should like to stress the need for the avoidance of barbiturates, bromides, and opiates, and allied narcotic drugs. Paraldehyde, drams 1 to 4, every 4 to 6 hours, is felt to be the best agent. Occasionally, one has to resort to chloral hydrate (gr. 10 to 30). Better still is the avoidance of all drugs by placing the patient in a suitable hospital and using measures other than drug therapy to procure the disappearance of delirious reactions." Vollmer[75,76] merely reports that "sedatives do not benefit patients with this disorder." On the other hand, Dow and Rosenbaum[31] state that "two of our patients had no relief on Artane and are now on atropine and phenobarbital." Corbin[17] asserts that "a feeling of nervousness, either unrelated to or caused by Artane, may be controlled by the administration of phenobarbital in doses of a quarter to a half grain t.i.d.," and that "those who have Parkinsonism appearing late in life, (that is, arteriosclerotic) in whom tremor is the predominant symptom . . . do not respond" to the usual "medical regimens. Fortunately, such persons are not greatly handicapped by their symptoms so that reassurance and mild sedation may be all that is required to carry them along with minimal discomfort." Denny-Brown[12], in discussing the toxic reactions that sometimes occur when large doses of Artane are used in patients over 50 years of age, states that "in true paralysis agitans, therefore, a simple sedative tonic, with phenobarbital at night, is often more satisfactory."

7. HOSPITALIZATION OF PATIENTS. Accurate stabilization of drug dosage may sometimes be achieved better by brief admission to the hospital, where the effects of a daily increase in dosage can be closely observed. The general management of the illness is much more exacting than that of diseases amenable to specific therapy. Many dissatisfied patients finally become discouraged and abandon treatment or drift off to the care of unorthodox practitioners[54].

8. THE "GENERAL RULE": Since we have no specific cure for Parkinsonism, and there is none in the offing, the purpose of all available therapy should be to render the patient as happy, active, and useful as possible. Hence, it is never wise to force a new remedy on a patient who is content with his present regimen of treatment[24].

9. JAMES PARKINSON'S METHOD OF TREATMENT. In order to reassure those who are discouraged at the present status of the drug therapy of Parkinson's syndrome it might be well to read of the following laborious method of treatment actually utilized by James Parkinson 137 years ago:

"At whatever period of the disease it might be proposed to attempt the cure, blood should be first taken from the upper part of the neck, unless contraindicated by any particular circumstance. After which vesicatories should be applied to the same part, and a purulent discharge obtained by appropriate use of the Sabine Liniment; having recourse to the application of a fresh blister, when from the diminution of the discharging surface, pus is not secreted in a sufficient quantity. Should the blisters be found too inconvenient, or a sufficient quantity of discharge not obtained thereby, an issue of at least an inch and a half in length might be established on each side of the vertebral columna, in its superior part. These, it is presumed, would be best formed with caustic, and kept open with any proper substance. Cork appears to be very appropriate to this purpose . . . and the intelligent will never fail to avail themselves of any opportunity of making trial of the in-

fluence of mercury, which as in so many instances, manifested its power in correcting derangement of structure. If . . . tonic medicines, and highly nutritious diet be directed, no benefit is likely to be thus obtained; since the disease depends not on general weakness, but merely on the interruption of the flow of the nervous influence to the affected parts"[60].

Other Therapies. 1. PHYSICAL THERAPY. In addition to drugs, physical therapy should be used as needed, and frequently is a useful adjuvant. Mild massage, heat and directed exercise once or twice weekly, may reduce muscle soreness and relax rigidity. Regular visits to the physiatrist afford continuity of therapeutic regimen and reinforce the physician's attempt to improve morale[4,16]. Rest is not helpful. Patients should be encouraged to keep up with their usual physical activities. However, violent physical exercise tends to increase muscle rigidity[13,54,79]. In far advanced Parkinsonism daily passive movements of all joints is essential. Hot baths will often relieve the disability in the joints and to some extent the stiffness[39]. Rabiner[48] states that "all of the drugs, old and new, that have been used for this disorder have some merit, and one may be a trifle more effective than others. None of them are of any value if the patient sits around and is inactive." Aside from the actual physical benefit derived from well directed physiotherapy, "these chronic sufferers need the constant assurance of their physician's interest, and regular treatments of this type bolster their confidence in the total therapeutic regimen"[17].

2. ELECTRO-CONVULSIVE THERAPY. Miller[54] states that "oculogyric crises, peculiar to the postencephalitic disease, may be very obstinate, but often show a reasonable response to amphetamine in full doses. When this fails, a course of electro-convulsive therapy may prove effective." Kalinowsky and Hoch[46] assert that "depressions and paranoid reactions of episodic character occurring in Parkinson's disease offer another important indication for ECT. We have treated several episodes in the same patient with great success. This is true not only for the psychosis but also for the neurological condition. These patients show an aggravation of their neurological dysfunction, while they suffer from emotional disturbances. One of our patients who walked fairly well became bedridden with severe rigidity of all four extremities with each psychotic episode. She was again able to walk quite well after ECT had cleared up the psychosis. These experiences are very interesting with regard to the question of organic or psychogenic disorder, and show that the amount of structural damage alone does not determine the degree of dysfunction in neurological disease."

3. SURGERY. As an adjunct to use of drugs, the position of surgery at present is unsettled[25]. Surgical procedures aim at abolishing tremor and replacing it by weakness or paralysis. Since most cases of Parkinsonism are progressive, careful selection of patients for surgery is vital. Surgery should probably be limited to patients under 50 years of age who are suffering from a gross tremor which is stationary or only slightly progressive, and is restricted to one extremity. Such rules would exclude about 95% of all patients. Surgical approaches to the problem have included the removal of the upper half of the caudate nucleus through an intraventricular approach[8], anterolateral spinal tractotomy at a cervical level[54], ligation of the anterior choroidol artery[15], and cerebral pedunculotomy[78], and others.

4. RESPONSIBILITY OF THE PHYSICIAN. The first physician to confront the pa-

tient and his family with the diagnosis has an important responsibility which may far outweigh his scientific knowledge of drug therapy. A hasty, pessimistic, or harshly worded statement regarding the hopelessness of the disease may make more difficult all subsequent attempts to encourage and help such patients. A reassuring and tactfully delivered discussion of the problem, in which the chronicity, slowness of progression and sparing of the mental faculties are emphasized, allays immediate fear and prepares the ground for an acceptable outline of the therapeutic program[17,32,35].

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PROCEEDINGS OF

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SESSION OF MARCH 16, 1954

The Measurement of Cardiac Output: A New Method* L. H. PETERSON, M. HELRICH, L. GREENE AND C. TAYLOR (Departments of Physiology, Surgery and Anesthesiology, University of Pennsylvania). A method permitting accurate measurement of instantaneous (response time 0.3 sec.) cardiac output in intact animals will be described. It is based upon a reliable device for injecting a known constant flow (F) of indicator (T-1824), of known concentration (C_i), into the ascending aorta. Simultaneously the concentration of the indicator in blood (C_o) is continuously sampled distally. Total instantaneous blood flow (F_t) is obtained from the relationship:

$$F_t = \left| \frac{C_i}{C_o} \times F_i \right| - F_i$$

The reliability of the method was tested with a model providing wide ranges of flow and velocity (S.D. $= \pm 1.06\%$, $r = 0.99$). The mixing problem was studied and mixing proved to be complete. In dogs (15 to 30 kg.) this method, the Fick, the classic dye dilution, the saline pulse, and the pulse pressure methods were compared. Measured flows ranged from 0.7 to 15 liters/minute. To date, 15 Fick determinations were done simultaneously with this method and when compared with the latter showed a random variation (S.D. $\pm$ 11%). The classic dye dilution determinations, obtained between two determinations with the reported method at 5- to 7-minute intervals, were compared when blood pressure, pulse pressure and respiration were similar. Simultaneous samples from multiple arterial sites showed identical dye concentrations, indicating complete mixing. Since the over-all reliability of this method appears high, variations in measured flow are assumed to be physiological. These variations, associated with respiratory and sinus arrhythmias, often occurring during the Fick and classic dye dilution determinations, are of greater significance in interpreting their variability than are lumped statistical treatments. These effects and the relationships of pulse pressure and flow will be discussed. The method appears applicable to man.

The Effects of Hypotension Induced by Intravenous Hexamethonium and Head-up Tilt upon Cerebral Hemodynamics in Man. HRANT H. STONE, M.D., THOMAS N. MACKRELL, M.D., and RICHARD L. WECHSLER** M.D. (Departments of Anesthesiology and Gastroenterology, Graduate Hospital and Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pensylvania). Induced hypotension by hexamethonium is becoming a useful clinical aid in the control of hemorrhage during surgery. Many believe the primary danger of such hypotension is cerebral

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**U. S. Puplic Health Service Fellow, The National Institutes of Health. This study was supported in part by The Wilson C. Laucks Memorial Research Foundation, The A. Atwater Kent Fund and The National Institutes of Health.

anoxia. This study was undertaken to discover the cerebral effects of hexamethonium induced hypotension. Ten recumbent subjects, chosen at random, were given from 50 to 225 mg. of hexamethonium bromide intravenously. In addition, for five of these patients, elevation of the head of the table 10 to 15 degrees was necessary to produce appreciable blood pressure fall. Cerebral blood flow was measured by the nitrous oxide method both before the the administration of the drug and after it had produced a stabilized hypotension. Cerebral oxygen consumption, respiratory quotient and vascular resistance were determined. Pulse and arterial blood pressure were measured continuously by means of a strain gauge manometer. The statistically significant decrease in mean arterial blood pressure from 117 to 62 mm. Hg ($p<0.001$) was accompanied by a significant decrease in cerebral vascular resistance from 2.4 to 1.3 mm. Hg/cc./100 gm./min. ($p<0.001$). This decrease in vascular resistance accounted for the maintenance of cerebral blood flow (53 to 47 cc./100 gm./min. — $p<0.3$). Arterial oxygen content decreased significantly from 15.8 to 14.7 vols% ($p<0.01$) as did internal jugular oxygen content (9.5 to 7.4 vols% — $p<0.001$) without significant change in the A–V oxygen difference (6.3 to 7.3 vols% — $p<0.1$). Arterial carbon dioxide content was not changed significantly. There were no significant changes in cerebral oxygen consumption, cerebral respiratory quotient, arterial and venous blood pH and carbon dioxide tension (pCO_2). These findings indicate that hexamethonium did not produce cerebral ischemia or cerebral anoxia, as reflected by its failure to change significantly either the cerebral blood flow or cerebral oxygen consumption.

A Function of the Spleen, as Disclosed by Labeling Studies of Hemoglobin Metabolism in Dogs. DAVID L. DRABKIN, ASHTON GRAYBIEL, J. K. COLEHOUR, VERA USDIN AND ANNA MAY DYCH (Dept. of Physiological Chemistry, Graduate School of Medicine, Univ. of Penna. and Naval School of Aviation Medicine, Naval Air Station, Pensacola, Fla.). In our earlier report (Am. J. Med. Sci., **223**, 694, 1952) attention was directed to the finding of unusual patterns of hemoglobin, hemin and stercobilin labeling (by means of glycine-2-C^{14}) in splenectomized dogs in comparison with intact dogs. These were unexpected findings, since splenectomized dogs were found by Drabkin and Graybiel (Fed. Proc., **10**, 177, 1951) to respond to altitude anoxia stress by an increase in hemoglobin and red cells very similarly to intact dogs.

In the present experiments, as before, thoroughbred beagle hounds of similar age and size were employed. In the splenectomized group, the operation was performed 6 to 8 months prior to the experiment. The simulated altitude was 18,000 feet, and blood and fecal samples were taken at more frequent periods than in the earlier work, so as to bring out features in labeling by means of glycine-2-C^{14} which may have escaped attention previously.

Both at sea level and altitude, the labeling curves of hemoglobin and dimethyl protoporphyrin (which represents the prosthetic group) were interpreted as representing a composite curve of 2 components, about 80% due to non-random destruction of red cells as a function of their age, and about 20% due to "random" destruction, that is, young and obsolescent cells destroyed indiscriminately.

Both at sea level and altitude, the labeling curves of hemoglobin in the splenectomized animal resemble closely

that described for random red cell destruction, as seen in human hemolytic disease. This does not mean that a hemolytic process is necessarily present, but that, in the dog, in the absence of the spleen the ability to destroy red cells non-randomly (as a function of their age) has been considerably lessened. The animals were in excellent health; no evidence of Bartonella infection was found in the splenectomized dogs. Further studies are in progress upon this newly uncovered positive function of the spleen.

Studies of Intravenous Reserpine in Man. A. M. SELLERS, M.D., AND J. H. HAFKENSCHIEL, M.D. (Hypertension Section, Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania). Swiss chemists isolated an alkaloid Reserpine from *Rauwolfia serpentina* in 1952. Reserpine was used to study the hypotensive properties of Rauwolfia in acute experiments.

Six normotensive and 20 severely hypertensive hospitalized patients had blood pressures, pulse rates, electrocardiograms, and ballistocardiograms recorded before and at intervals during the experiment. Reserpine (1.6 to 5.6 mg.) was given by intravenous infusion in 60 minutes. The effective dose was found to be 60 to 80 micrograms/kilogram.

The 6 normotensive patients had an average blood pressure of 111/68 before Reserpine, 109/62 at the end of the infusion and 96/52 at the maximum fall 4 hours later. Only one of the six had no fall. The 20 hypertensive patients had an average blood pressure of 202/125 before Reserpine, 181/112 at the end of the infusion and 144/91 at the maximum fall 4 hours later. In several instances, the hypotensive levels persisted for 24 hours. Eighteen of the 20 patients had a fall in pressure of at least 40 systolic and 10 diastolic, 10 patients during the infusion and 8 after an average period of 4 hours after the infusion. Pulse rate, electrocardiogram, and ballistocardiogram were unchanged during the infusion.

Side effects in both normotensive and hypertensive patients were: sedation, relaxation, and nasal congestion in almost all; nausea and emesis were less frequent. Seventeen of the hypertensives and 5 of the normotensives showed postural hypotension.

The hypotensive action of the pure alkaloid Reserpine in the dosage range 60 to 80 micrograms/kilogram has been demonstrated. Its effectiveness in normotensive patients suggests that it must interfere with normal blood pressure regulating mechanisms and is not necessarily a specific antagonist of pressor mechanisms in essential hypertension. The 4-hour delay in greatest hypotensive response suggests that Reserpine may undergo degradation to yield the effective component. The slowness of the development of the hypotensive effect permits marked falls in pressure with little subjective discomfort and suggests that Reserpine is worthy of further study in the treatment of crises of severe hypertension.

BOOK REVIEWS AND NOTICES

PERIPHERAL NERVE INJURIES. By WEBB HAYMAKER, M.D., Chief, Neuropathology Section of the Armed Forces Inst. of Path., and BARNES WOODHALL, M.D., Prof. of Neurosurgery, Duke Univ. School of Med. 2nd ed. Pp. 333; 272 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $7.00.

THIS edition of a previously excellent monograph has been thoroughly revised.

The text is divided into four sections: the *first* deals with Innervation, the *second* with examination of the patient, the *third* with a clinicopathological classification of peripheral nerve injuries and causes and the general symptomatology of such injuries, and the *fourth* with the clinical features of individual plexus and peripheral nerve injuries.

In the present edition greater emphasis has been given to such topics as pain, trick movements, contracture, electromyographic studies and Hoffman-Tinel's sign. There is a new chapter on the different degrees of nerve injury in terms of pathological changes. The illustrations of movements tested in the neurological examination and the course and distribution of the various nerves and plexuses are superb.

This monograph is invaluable to students, practitioners, or nerve specialists and particularly any surgeon who treats injuries involving or contiguous to peripheral nerves.

M. S.

A BIBLIOGRAPHY OF THE WORLD LITERATURE ON BLOOD PRESSURE 1920-1950. VOLUME I, AUTHORS AND TITLES. VOLUME II, AUTHOR INDEX AND TITLE INDEX. VOLUME III, ABSTRACTS. Edited by ERNEST K. KOLLER AND JACOB KATZ, Bureau of Applied Social Research and School of Public Health, Columbia University. Boston: Recess Commission on Hypertension, Commonwealth of Massachusetts, 1952. Price, $5.00, for the three volumes.

INVESTIGATORS in the field of hypertension and physicians with a special interest in this subject will find these volumes of great value to them. The compilation represents a by-product of a current investigation into the epidemiology of essential hypertension being carried on at Columbia University, sponsored and financed by the Commonwealth of Massachusetts. The first volume is an alphabetical listing, by senior author, of approximately 17,000 titles. The second is an alphabetized index to the co-authors in the first volume, and an index to all of its titles. The third consists of approximately 1500 abstracts of titles from Volume I. A considerable portion of these are concerned with the incidence, prevalence, trend and distribution of hypertension according to the various factors customarily treated in conventional descriptive epidemiology.

T. D.

PITKIN'S CONDUCTION ANESTHESIA. By GEORGE P. PITKIN, M.D., F.A.C.S., F.I.C.A. Edited by JAMES L. SOUTHWORTH, M.D., Attending Surgeon, East Tennessee Tuberculosis Hospital and East Tennessee Baptist Hospital, Knoxville, Tennessee; ROBERT A. HINGSON, M.D., Professor of Anesthesia, Western Reserve University, Cleveland, Ohio; and WINIFRED M. PITKIN, M.D., Assistant in Surgery to the late George P. Pitkin. 2nd ed. Pp. 1005; 585 ills. Philadelphia: J. B. Lippincott Co., 1953. Price, $22.50.

THE editors have compiled into one edition the most complete treatment of regional anesthesia that has ever been published. They have reorganized this edition with several improvements.

The second chapter "The Vertebral Canal and Its Contents" is a most welcome addition and this may also be said of the chapter "The Clinical Pharmacology of the Local Anesthetics". This latter chapter brings the reader up-to-date on the newest theories of mechanism of local anesthesia as well as the use of newer local anesthetic agents. The addition of the chapter "Complications of Conduction Anesthesia (cause, prevention, treatment)" is excellent.

In the revision of this book the editors failed to include a section on shock. This subject should be included in all textbooks of anesthesia and surgery.

This textbook is most complete and is an excellent reference book.

L. K.

EXTRASYSTOLES AND ALLIED ARRHYTHMIAS. By DAVID SCHERF, M.D., F.A.C.P., Associate Professor of Medicine, New York Medical College, and ADOLF SCHOTT, M.D., M.R.C.S., Medical Officer in Charge of the Cardiographic Department, Queen Mary's Hospital for the East End, London. Pp. 531; 213

ills. New York: Grune & Stratton, 1953. Price, $15.50.

THIS exhaustive text on the subject of extrasystoles and allied arrhythmias is based on the authors' years of interest and study of the subject dating back to their contacts 30 years ago with Prof. Wenckebach and Prof. Rothberger. They believe the most important feature of these disturbances of rhythm to be the fact that a dominant rhythm is interfered with, or replaced by, contractions due to abnormal impulses. The impulses can be abnormal either as to their site of origin, ectopic; or their time of occurrence, premature; or both. In the vast majority of instances they are ectopic. Within this great group of arrhythmias, only those having accurate coupling to the preceding beat should be termed extrasystolic. In these the stimulus is considered to be a more passive phenomenon, dependent upon, and precipitated by, the preceding beat, in contrast to the active formation of automatic impulses in parasystolic arrhythmias. Paroxysmal tachycardia, auricular flutter and auricular fibrillation are included within the scope of these definitions. The authors believe that auricular flutter and fibrillation are due, not to circus movement, but to frequent impulses originating in a circumscribed focus. The discussion of all of these arrhythmias is a very detailed one and includes a wide view of the literature. It should prove to be of interest to cardiologists and physiologists. T. D.

GLOBAL EPIDEMIOLOGY. VOLUME 3. THE NEAR AND MIDDLE EAST. BY JAMES S. SIMMONS, M.D., PH.D., DR.P.H., SCD., TOM F. WHAYNE, M.D., M.P.H., DR.P.H., GAYLORD W. ANDERSON, M.D., DR.P.H., HAROLD M. HORACK, B.S., M.D., RUTH ALIDA THOMAS, M.P.H. AND COLLABORATORS. Pp. 357; illustrated. Philadelphia: J. B. Lippincott Co., 1954. Price, $12.00.

THIS is the third volume of a series outlining the cause, prevention and epidemiology of diseases, largely tropical, as encountered in various parts of the world. Of particular interest and value are the splendid descriptions for each country of geography and climate, population and socio-economic conditions, environmental conditions, sanitation and health service and medical facilities which so largely determine disease occurrence and management. The first volume dealt with India, the Far East and the Pacific Area; the second volume with Africa and its adjacent islands; this volume includes the countries of the Near and Middle East from Turkey to Afghanistan and including the Arabian Peninsula. The growing importance of such information in commercial, political and military spheres cannot be overemphasized. The authors are to be congratulated upon the splendid fulfillment of their task. R. K.

PHYSIOLOGY OF THE EYE. BY FRANCIS HEED ADLER, M.A., M.D., Prof. of Ophthalmology, University of Pennsylvania. 2nd ed. Pp. 734; 329 ills., 3 in color. St. Louis: C. V. Mosby Co., 1953. Price, $13.00.

ADLER'S Physiology of the Eye is the outstanding American contribution in this field. The difficult subject material is lucidly and concisely presented. The text is well organized, well illustrated, and complete. The author has exercised admirable restraint in limiting the clinical aspects to a minimum. The second edition, which appears rather soon after the first, contains the more recent advances in ocular physiology. No ophthalmic library is complete without this volume. G. G.

FIBROCYSTIC DISEASE OF THE PANCREAS. Edited by MARTIN BODIAN, M.D. Pp. 244; 133 ills. New York: Grune & Stratton, Inc., 1953. Price, $9.50.

THIS is a comprehensive monograph on fibrocystic disease of the pancreas. The literature is critically reviewed, beginning with early descriptions of steatorrhea, the papers which emphasized the pancreatic disturbance, followed by those which introduced the concept of the generalized disease. Special features are also discussed and include the findings of chest roentgenograms, results of tests of enzyme activity and absorption studies, treatment, and etiology. Other chapters deal with clinical aspects, familial incidence, and its pathologic picture with emphasis on disordered mucous production (mucosis). The text is written in a readable form, and the illustrations are excellent. Anyone interested in fibrocystic disease of the pancreas will find this a valuable reference work. C. Z.

DIE KREUZSCHMERZEN DER FRAU. BY PROF. DR. HEINRICH MARTIUS. 4th ed. Pp. 166; 73 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 19.50.

THE fourth edition of Martius' text on low back pain in women is divided into two parts,

the first of which deals with the anatomical patho-physiology of back pain and the second with clinical investigation and management.

The mechanisms for the production of low back pain are considered in detail and the discussion on neurophysiology is particularly good. A rather interesting suggestion that a small female pelvis can be responsible for postural back pain is discussed. The analysis of the mechanical causes due to posture and dysfunction of the supporting structures also is excellent. He points out, however, that emotional factors may play an important part in the production of pain and states that only about one-third of women have significant organic findings which might produce the symptoms while in another third the examinations all were normal. Organic changes may also be found in women without complaints.

No unusual suggestions for the management of low back pain are presented but nevertheless this is an instructive and an important book which should interest any physician confronted with the problem because it brings together in one volume a fairly complete evaluation of the subject. J. W.

PNEUMOCONIOSIS ABSTRACTS. VOLUME 1. Reprinted from the Bulletin of Hygiene for the years 1926 to 1938 inclusive. Pp. 347; illustrated. New York: Pitman Publishing Corp., 1953. Price, $12.50.

THIS volume is the first of two which will contain all abstracts of papers relating to pneumoconiosis that have been published in the Bulletin of Hygiene from the time of its first appearance in 1926 to the end of 1950. The present volume covers the period 1926 to 1938. They are arranged by topics in twelve chapters devoted to the several types of pneumoconiosis, sampling and measurement of dusts and of their significant properties, protective measures against pneumoconiosis, legislation on the subject and book reviews. Research workers, teachers and students will find this an invaluable reference work. R. K.

THE SUPRARENAL CORTEX. Edited by J. M. YOFFEY. Pp. 232; 49 ills. New York: Academic Press, Inc., 1953. Price, $6.80.

THIS volume contains the Proceedings of the Fifth Symposium of the Colston Research Society, held at the University of Bristol, England, in April 1952. There are 20 excellent papers which summarize much of the recent clinical and laboratory information dealing with the steroid hormones. Included are discussions of the chemistry of ACTH; the structure of the adrenal cortex and the nature and control of its secretory activity; the adreno-genital relationship; the role of the adrenal glands in infection and intoxication; the adrenal steroids and personality disorders; tissue responses to ACTH and cortisone; and steroid hormones in relation to skin grafting. Although there are now published numerous articles and discussions of this type, several of the sections in this volume will still be of value to workers in this broad field. C. Z.

ON APHASIA. BY SIGMUND FREUD. Translated by E. Stengel, Reader in Psychiatry, University of London. Pp. 105; 10 ills. New York: International Universities Press, 1954. Price, $3.00.

FREUD'S monograph on aphasia was the first of his writings dealing with mental activities and thus provides a link between his studies in organic neurology and his psychoanalytic period. He challenges the then current theories of localization and insists on the compatibility of the functional, dynamic with the localizatory approach. He adopts as a guiding principle Hughlings Jackson's doctrine of functional retrogression, which later underlies the genetic propositions of psychoanalysis. Freud's discussion of paraphasia (mistaken use of words) reads like a prelude to the explanation of errors and slips of the tongue in his later "Psychopathology of Everyday Life." Throughout the book Freud's preference for concepts implying dynamic processes rather than static conditions is conspicuous. Dr. Stengel has rendered a real service to the English-speaking world by supplying an excellent translation of this most significant forerunner of Freud's later work. E. S.

EINFÜHRUNG IN DIE AUGENHEILKUNDE. BY PROFESSOR DR. MED. P. A. JAENSCH, Head of the Municipal Eye Clinic at Essen and Professor of the Medical Academy at Dusseldorf. 2nd, improved ed. Pp. 248; 197 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 22.

THIS book is written primarily as an "introduction to ophthalmology" for medical students, but it will also be of great help to any general practitioner who wishes quickly to review the subject and does not have the

time to thoroughly study the voluminous classical textbooks.

The first edition appeared in 1947, followed by the present 2nd edition.

The author has successfully condensed the topic to a mere 235 pages. But the condensation presents a very clear and basic picture, so that a student can readily build it up by further postgraduate studies if he so desires.

The book is printed and edited in the fine style and tradition of the Thieme Verlag and very readable.

Such a book should remove the "horror" of ophthalmology so frequently found among students. This volume is moreover especially valuable because it devotes an unusually large section to the physiology and pathology of the light- and color-sense. At the end of the book there is a short explanation of the ophthalmological nomenclature; which, with its many Greek derivations, is often difficult for the student to remember. W. P.

Advances in Cancer Research. Vol. I. Edited by Jesse P. Greenstein and Alexander Haddow. Pp. 590; 45 ills. New York: Academic Press, Inc., 1953. Price, $12.00.

This is the first volume of a new series of reviews covering the advances in various branches of cancer investigation. The following topics are included: Electronic Configuration and Carcinogenesis; Epidermal Carcinogenesis; The Milk Agent in the Origin of Mammary Tumors in Mice; Hormonal Aspects of Experimental Tumorigenesis; Properties of the Agent of Rous No. 1 Sarcoma; Applications of Radioisotopes to Studies of Carcinogenesis and Tumor Metabolism; The Carcinogenic Aminoazo Dyes; The Chemistry of Cytotoxic Alkylating Agents; Nutrition in Relation to Cancer; and Plasma Proteins in Cancer.

The discussions are basic, comprehensive, and timely. This and succeeding volumes will be welcomed as valuable references for workers in cancer research. C. Z.

Dystrophia Musculorum Progressiva. By Prof. Dr. P. E. Becker. Pp. 311; 101 ills. Stuttgart: Georg Thieme Verlag, 1953 (Grune & Stratton, New York, U. S. Agents). Price, DM 28.50.

On the basis of studies of 259 personally observed cases, the author has shown that Erb's opinion that progressive muscular dystrophy is a single entity is incorrect. The author describes three clinical types: a dominant one, a recessive autosomal and a recessive sex-linked form. Thus the fact that the shoulder girdle or descending form and the pelvic girdle form never occur together speaks for the basic difference of these two types. The author's conclusions are based on extensive studies of families for several generations. Clinical data are detailed and well presented. The conclusions drawn are reasonable under the premises. The work, therefore, represents a valuable contribution to our knowledge of the subject from the genetic and the clinical standpoints. There are numerous references to the literature and a good historical review. M. M.

Medical Psychology. By Paul Schilder. Translated and edited by David Rapaport, Austen Riggs Center, Stockbridge, Mass. Pp. 428; 9 ills. New York: International Universities Press, Inc., 1953. Price, $7.50.

This book is a translation from the German of a book written by the author in 1923, when he was Professor of Psychiatry in the University of Vienna. The contents include The Theory of Perception; Action and Language; Memory; Instincts, Volition and Action; and The Ego and Personality.

When written the book aimed to correlate experimental and clinical psychology, psychoanalysis, psychiatry and clinical and research neurology. Hence it is a timely contribution as these fields attempt to collaborate and consolidate their knowledge as never before in the urgent need to understand and treat mental illness. The translator has made generous and useful addenda in the form of footnotes, bibliography, foreword, and the reprinting of a memorial address. O. E.

Diseases of Women. By Robert James Crossen, A.B., M.D., F.A.C.S., Prof. Clin. Gyn. and Obst., Washington Univ. School of Medicine. 10th ed. Pp. 935; 990 ills. 40 in color. St. Louis: C. V. Mosby Co., 1953. Price, $18.50.

The 10th edition of "Diseases of Women" was prepared by Robert James Crossen who has been junior author of the volume since 1930. A section on endocrine relations of the ovarian cycle was written by Willard Allen and another on the radiation therapy of pelvic cancer by A. N. Arneson. The material is presented in a conventional manner beginning with anatomy, physiology and gynecologic examination and then proceeding to a detailed discussion of the disease proc-

ess which may affect each portion of the female reproductive organs. Many of the 990 illustrations are clearly reproduced and a distinct aid in demonstrating the lesions discussed or methods for diagnosis and treatment but many are retained from earlier editions and should be replaced or in some instances deleted.

The author has attempted "to present for the student the basic facts and salient developments on the biologic and physiologic investigations which are making history in the gynecologic field, and to bring to the practitioner a comprehensive systematic judicial consideration of the diagnostic and therapeutic aids made possible by these great advances in knowledge." The former he does reasonably well but the multitude of references has not been carefully selected and edited and many old and disproven concepts are presented as facts. For instance, "myoma heart" is presented as though there was such an entity. In his second aim, he fails completely because he so often simply lists and describes treatment after treatment, many of which are worthless, for each condition he discusses and only rarely does he analyze the results and indicate which he has found successful. For instance, the therapeutic recommendations for the treatment of trichomoniasis by 8 different authors are presented and in addition numerous drugs and preparations are mentioned but the author does not describe how to treat this common condition. The recommendations for treatment of primary dysmenorrhea are presented in the following order: hypnosis, mental and physical hygiene, diet, antispasmodics, vasodilators and endocrine preparations. Simple analgesics, such as aspirin compound, are not mentioned.

While this book contains a tremendous amount of worthwhile material its main value is as a reference for experienced gynecologists. It is too general and uncritical to serve a very useful purpose as a text for students or as an aid to the family physician. J. W.

HYPERSPLENISM. A CLINICAL EVALUATION. By CYRUS C. STURGIS, M.D. Pp. 97; 6 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $3.25.

DR. STURGIS is internationally recognized as an authority on hematology. His present treatise is primarily a clinical evaluation of hypersplenism. For this monograph, he has drawn on the extensive experience of himself and his colleagues at the Simpson Memorial Institute for Medical Research.

Chapters deal with the structure and function of the spleen; changes which result after its removal from normal mammals; the various theories as to the mechanism of hypersplenism; classification and types of hypersplenism; diagnosis; indications for and contraindications against splenectomy.

This is a lucidly written volume which should be helpful to medical students, internists, and surgeons alike. C. Z.

PRAKTISCHE ARBEITSPHYSIOLOGIE. By PROF. GUNTHER LEHMANN, Max-Planck Institute, Dortmund. Pp. 343; 145 ills. Stuttgart: Georg Thieme Verlag, 1953 (Grune & Stratton, New York, U. S. Agents). Price, DM 29.70.

THIS book concerning "working physiology" deals with physiological functions. It is written not only for medical students but also for other related sciences. The fundamental data are presented which permit a clear understanding of physiological changes during work. The treatment is, however, a practical one. Therefore both technicians and more advanced students will find it useful. A good appendix is included. Both the physiology of work and references to the associated science of psycho-physiology are treated. This book can be recommended. M. O.

AN ATLAS OF PELVIC OPERATIONS. By LANGDON PARSONS, M.D., Prof. of Gynecology, and HOWARD ULFELDER, M.D., Asst. Clin. Prof. of Gynecology, Harvard Medical School. Pp. 231; 197 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $18.00.

THIS book is one of the most comprehensive and usable texts on operative gynecology which has yet been prepared. It includes not only the details of gynecologic operations but the general surgical procedures which the gynecologist must of necessity perform. In the latter category operations on the bladder and ureter, the large and small bowel and the technique for repair of various types of herniae are described. The radical operations for the treatment of malignancy are also presented. The authors have wisely not attempted to include every gynecologic operation but present only those which they utilize in their own work. Obsolete and rare procedures are not presented.

The illustrations are line drawings which are clear, easily interpreted and from which unnecessary detail has been omitted. The text is concise and the short description of

each step is placed adjacent to the illustration it accompanies. Each section is introduced by a general discussion of the problem to be considered but specfiic details of the disease processes for which the operations are designed are avoided because indications and contraindications may change from time to time while the steps in the procedure remain unaltered.

This outstanding text should be available to gynecologists and general surgeons in training as well as those in practice because both can learn much from it. J. W.

CLINICAL CARDIOLOGY. Edited by FRANKLIN C. MASSEY, M.D., Asst. Prof of Medicine, Hahnemann Medical College of Philadelphia. Pp. 1100; 212 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $13.50.

IN this rather comprehensive text, Dr. Massey, along with an imposing list of collaborators, has done an excellent job in correlating strict cardiology with the allied specialties. One chapter of particular interest is devoted entirely to surgery of congenital and acquired lesions of the heart concerning which the most recent thoughts are elaborated. Chapters on Metabolic and Endocrine Aspects of Heart Disease, Anesthesia and Surgery in the Cardiac Patient, and The Heart in Pregnancy fill out a rather complete text. Threaded through the subject matter is a discussion of related patho-physiology and hemodynamics in a clear and concise manner. Each chapter, of which there are twenty-eight, is followed by an up-to-date bibliography. The tables and illustrations are particularly pertinent.

All in all, although there are many good cardiologic texts on the market, this one seems, to the reviewer, to be well worth having in one's library of current books.

G. M.

YEAR BOOK OF MEDICINE, 1953-1954. Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., GEORGE B. EUSTERMAN, M.D., AND ROBERT H. WILLIAMS, M.D. Pp. 736; 127 ills. Chicago: Year Book Publishers, 1953. Price, $6.00.

THE current volume of this series is comprised of abstracts of articles published in various journals during the period May, 1952 to May, 1953. The editors are recognized authorities in the respective fields surveyed. They have again produced a competent sifting of an extensive medical literature which should be helpful to all who are interested in internal medicine. C. Z.

TASCHENBUCH DER VITAMINTHERAPIE IN DER FRAUENHEILKUNDE. BY H. O. KLEINE, M.D. Pp. 139. Stuttgart: Hippokrates-Verlag Marquardt & Cie., 1953. Price, DM 8.

THE small text presents a fairly complete analysis of the vitamins and their influence on obstetric and gynecologic disorders and in newly born infants. In the general discussion, the functions of the vitamin substances, their occurrence in foodstuffs including human milk, and the factors which are responsible for the variations in the content of the diet are considered. The manifestations of vitamin deficiencies are described and the relationships between these substances and mineral metabolism, hormone function and sexual function in the female is considered. This book should serve its purpose as a reference for the general practitioner and for the gynecologist quite adequately. J. W.

THE HEART BEAT. BY ALDO A. LUISADA, M.D., Assoc. Prof. of Medicine, Chicago Medical School. Pp. 527; 311 ills. New York: Paul B. Hoeber, Inc., 1953. Price, $12.00.

As the author states in his preface, no comprehensive work has been published on graphic methods of recording the heart beat since 1924. This volume includes all methods at present used in the graphic representation of cardiovascular phenomena.

The book is divided into four parts. The first concerns an historical outline of the development on graphic methods of study as well as some physiology pertaining to the heart beat. Part II concerns normal tracings of various graphic methods such as phonocardiography, ballistocardiography, esophagocardiography, arterial pulsations, cardiomanometry, electrokymography, radiocardiography, spirography, electrocardiography and many others. The techniques used and the interpretation of the graphs are discussed. Part III considers physiologic variants of the graphic tracings in the normal adult, the fetal heart, and in the aged particularly. Included is a section dealing with modifications of tracings caused by drugs and physiopathologic variants. Part IV deals entirely with the practical clinical applications of these graphic methods which include valvular disease, congenital malformations, heart failure and others.

The illustrations are extremely good and this volume must be considered an excellent text as well as reference to that which is known concerning graphic methods at the present time. G. M.

PREGNANCY WASTAGE. Edited by EARL T. ENGLE. Pp. 254; 81 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $7.75.

THE total infant mortality during pregnancy and after birth is difficult to calculate but the rate has not fallen as rapidly as has the number of maternal deaths. The term *Pregnancy Wastage* is used to indicate the total fetal loss after conception and this volume includes the papers and the discussions presented at a conference on that subject sponsored by the National Research Council Committee on Human Reproduction. The participants, all specialists in the field of reproduction, included anatomists, biologists, chemists, pathologists, physiologists and veterinarians as well as clinicians. The subject material concerns all aspects of fetal loss such as fertilization, abortion, toxemia of pregnancy and premature labor.

The fact that the essayists and the discussants were selected because of their interest in the problem makes the material highly authoritative, by the same token much of it is also experimental and not as yet clinically applicable. There is, however, much of interest and value to the clinician as well as the investigator and many of the papers contain considerable material which can be applied directly to practice. J. W.

EVALUATING RESEARCH AND DEVELOPMENT. Edited by IRVING R. WECHSLER AND PAULA BROWN. Pp. 103. Los Angeles: Institute of Industrial Relations, University of California, 1953. Price, $1.65.

THIS book resulted from a conference of research administrators which was held at the University of California, Los Angeles, on May 10, 1952. The purpose of the conference was "to determine methods of evaluating research and/or development output and to propose methods of establishing the effectiveness of the individual working alone or as a member of a group."

There is an interesting discussion on the criteria of evaluation by Dean L. M. K. Boelter. He states: "The native character of the individual and his response to the research or development environment are fundamental to his effective performance. Whether working alone or in a group, his individuality is his greatest assist in the creation, planning, and execution of the task at hand."

The annotated report of the conference proceedings is presented in two main sections: A) The Formulation and Definition of Research and Development Objectives, and B) The Evaluation of Individual Group Performance with Reference to Objectives (Ideal Performance).

Anyone familiar with research and research workers will appreciate the magnitude of the task undertaken by this conference. The report is to a large extent made up of excerpts and is thereby more difficult for the reader. However, administrators and research workers will find a number of interesting and provocative concepts set forth in this small volume. C. Z.

MEDICAL HISTORY OF THE SECOND WORLD WAR. SURGERY. Edited by SIR ZACHARY COPE, B.A., M.D., M.S., F.R.C.S. Pp. 772; 96 ills. London: Her Majesty's Stationery Office, 1953. Price, 80s.

THIS large volume is a comprehensive and detailed account of English surgery during World War II. It is compiled and edited by Sir Zachary Cope, but it has been written by the most eminent British surgeons, most of whom are recognized specialists in their fields. It is a history which traces the advances in surgical therapy and management beginning in the dark days of the early war and continuing to the end of the war in 1945.

In the gradual evolution of wound therapy, the English experience is in many respects similar to our own. British experience has been greater than ours in such injuries as burns, the crush syndrome, and blast injury. The sections on these lesions are probably the most comprehensive to be found in the English language.

The sections on blood transfusions and the organization of the transfusion service is a chronology of great value. The description of the rehabilitation program, especially of the patients suffering with spinal cord injuries, is the evolution of an idea that is the basis of our present day rehabilitation efforts. No surgical specialty is neglected; there are sections on neurosurgery, thoracic surgery, plastic surgery, orthopedic surgery, *et cetera,* all written by outstanding specialists. The volume is well illustrated, the plates being in color in many instances.

This is more than a history. It is an effort to review and assess the lessons learned from

the surgical experience of the late war and to make them available to the peace-time surgeon. L. F.

LEISTUNGSSTEIGERUNG: LEISTUNG, UBERMÜDUNG, GESUNDERHALTUNG. By PROF. DR. MAX HOCHBEIN, Chief, Med. Clinic, Ludwigshafen on the Rhein, and DOZ. DR. IRENE HOCHBEIN-SCHLEICHER. 3rd ed. Pp. 283; 53 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 27.00.

THIS is an unusual book, the product of an unusual foundation: The First German University Institute of Occupational and Performance Medicine in Leipsig, dedicated to the study of human health and human efficiency in declining years. The most important aspect of gerontologic thinking and practice has to do with preservation of an increase of efficiency of the aged even more than the prolongation of human life: putting more life into years, not just putting more years into life. Physicians who read German will find in this the 3rd edition much of practical value for their geriatric practice. R. K.

EINFÜHRUNG IN DIE INNERE MEDIZIN. By DR. HANS JULIUS WOLF, Prof. of Internal Medicine, Univ. of Göttingen. 5th ed. Pp. 714; 90 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 35.

TEXTBOOKS of internal medicine are steadily increasing in size. Three current American texts average about 1600 pages. In Europe a number of standard texts for students have long been published in two volumes, aggregating well over 2,000 pages. The author of this textbook set himself the task of providing students with a briefer exposition and yet not so brief as to fall into the errors of a compendium. He also sought to give the practitioner a text for rapid practical reference and review. He has succeeded rather better than would have seemed possible. At least the popularity of the work testifies to its acceptability: this is the 5th edition issued less than 12 years after the first. It differs from most American texts in that diseases of the nervous system and psychoses have not been included. In rather sharp contrast to current texts is the fact that it is the work of one author. Herein lies a major weakness, in that no one man today can thoroughly master all aspects of internal medicine. Nevertheless it is astonishing how well most of the book is written. In form and arrangement it is even superior to the usual American text. The illustrations are excellent. Students and physicians who read German will find this a useful text. R. K.

ADVANCES IN VIRUS RESEARCH, VOLUME I. Edited by MAX A. LAUFFER AND KENNETH M. SMITH. Pp. 362; 28 ills. New York: Academic Press, Inc., 1953. Price, $8.00.

THIS is the first volume of a projected new series of reviews on viruses which affect animals, insects, plants and bacteria as well as man. Attention is to be focused primarily on the virus rather than the disease. The editors are eminently qualified for this task, and the present volume sends the series off on an auspicious start. The contributions include The Properties of Bacteriophages (by H. T. Epstein), Interactions between Viruses and Virus Strains (by C. W. Bennett), Transmission (by L. M. Black), Insect Viruses (by G. H. Bergold), Multiplication of Influenza Virus (by W. Henle), Poliomyelitis (by J. L. Melnick), Purification and Properties of Animal Viruses (by D. G. Sharp), and Virus Nucleic Acids (by R. Markham). C. Z.

FANCONI AND WALLGREN'S TEXTBOOK OF PEDIATRICS. Edited by W. R. F. COLLIS, M.A., M.D., F.R.C.P., Lecturer in Pediatrics, Dublin University. Pp. 1104; 441 ills. New York: Grune & Stratton, 1952. Price, $19.50.

THIS textbook was originally published in German by a number of prominent European pediatricians. The present edition is the English translation which has been revised to include more recent material. It is well written, but employs many terms which are unknown or poorly understood in this country. Sections on therapy occasionally seem inadequate. The illustrations, both black and white as well as colored, are excellent. The book would appear to be most valuable to pediatricians and pediatric residents for its presentation of the European approach to child care. R. H.

WONDERS OF MODERN MEDICINE. By STEVEN M. SPENCER. Pp. 276. New York: McGraw Hill Book Co., 1953. Price, $4.00.

THE reviewer approaches this book with a distinctly personal interest in the book and its author. When he was Chairman of the

Committee on Publicity of the 1935 Sessions of the American College of Physicians in Philadelphia, he met a young reporter from the Philadelphia Evening Bulletin covering his first major medical meeting. The interest in medicine, then kindled, and the presentation of medical advances to the layman became the life's work of that reporter. You will meet him at every important medical meeting, and, if he knows you well, he will probably ask your opinion about some paper or author. Weeks later there will appear an article in a lay publication, making available to all in intelligible, readable English some important medical advance. The present volume contains 20 such articles, most of which first appeared in The Saturday Evening Post, but brought up-to-date wherever necessary. All of them are timely and accurate, manifesting the journalist's keen sense of what is newsworthy, but never offending the scientist's concern for propriety and truth. In recommending this book to lay readers, the reviewer also wishes to congratulate Mr. Spencer on his interpretation of medicine and of doctors to the lay public. R. K.

GUIDE TO THE CLASSIFICATION AND IDENTIFICATION OF THE ACTINOMYCETES AND THEIR ANTIBIOTICS. By SELMAN A. WAKSMAN, Prof. of Microbiology and HUBERT A. LECHEVALIER, Asst. Prof. of Microbiology, Rutgers University. Pp. 246. Baltimore: The Williams & Wilkins Co., 1953. Price, $5.00.

FOR many years the major author and his associates studied this group of soil microorganisms without exciting general interest. When, however, they discovered that one genus, the *Streptomyces,* is a "gold mine" of antibiotics, the literature became flooded with reports of new (?) species and of antibiotics produced by them. The result was a state of utter confusion. Because it restores order in this chaotic field, this volume is indeed well timed.

Following the format of Bergey's Manual so well known to bacteriologists, almost 150 species of *Streptomyces* alone are characterized, including the presence or absence of antibiotic properties. Of equal value is a key to more than 100 antibiotics followed by brief descriptions in alphabetical order. This volume is not a laboratory guide to species identification since it omits methodology; rather, it is a dictionary of the actinomycetic antibiotics for the specialized student and investigator. E. S.

PHARMACOLOGY AND THERAPEUTICS. By ARTHUR GROLLMAN, PH.D., M.D., Prof. and Chairman, Dept. of Exper. Medicine, Southwestern Medical School, University of Texas. 2nd ed. Pp. 866; 127 ills. Philadelphia: Lea & Febiger, 1954. Price, $10.00.

THE author set himself the task of writing a book that would satisfy the experimental pharmacologist with broad theoretical interests, the student who needs a basic course to teach him how to use drugs rationally and successfully, and the practitioner who wishes to keep abreast of developments. He has succeeded extremely well in satifying all three, which probably accounts for the call for the second edition within three years of the first. The book is a worthy successor to the splendid text of Cushny, which it replaced. R. K.

LIVING WITH A DISABILITY. By HOWARD A. RUSK, M.D., Director, Institute of Physical Medicine and Rehabilitation, and EUGENE J. TAYLOR. Pp. 207; 281 ills. New York: The Blakiston Co., 1953. Price, $3.50.

THIS is the first book for the physically handicapped and their families which brings to their attention gadgets and devices that will help the disabled in the performance of the daily activities of life, work and play. The 281 photographs and drawings tell their own story with just enough help in a simple and concise text to get the message across. All physicians will here find much practical information that they can pass on to their patients. There really should be a copy in the home of every disabled person. R. K.

AN INTRODUCTION TO HUMAN BIOCHEMICAL GENETICS. By H. HARRIS, M.A., M.D., Galton Laboratory, University College, University of London. Pp. 96; 33 ills. New York: Cambridge University Press, 1953. Price, $2.75.

IN this brief monograph, Dr. Harris summarized the information gained in human biochemical genetics since the time of Garrod. Emphasized is the need of a precise understanding of the known biochemical mechanisms. Aspects treated in detail are those human metabolic traits which have been most thoroughly investigated. Included are discussions of cystinuria, phenylketonuria and alkaptonuria. Under the hemoglobin variants is a very complete discussion of sickle-cell disease.

Dr. Harris begins his monograph with a discussion of inborn biochemical variation and Mendelian heredity in man. He ends the treatise with a brief description of variation in the manifestations of hereditary characteristics.

The book is very well written and is supported and documented by explanatory tables and graphs. An extensive bibliography is included. D. K.

STANDARD METHODS OF CLINICAL CHEMISTRY, VOLUME I. Edited by MIRIAM REINER. Pp. 142; 7 ills. New York: Academic Press, 1953. Price, $4.50.

THIS is the initial volume of a projected series to be published by the American Association of Clinical Chemists. Its purpose is to summarize authoritatively the various methods employed in clinical chemistry. The principle underlying each method is delineated followed by precise descriptions of the preparation of reagents and the sequence of procedures. The range of normal and pathological results is indicated for each of the 24 methods included. An especially valuable feature is the inclusion of comments dealing with special precautions to be observed in the performance of the respective tests.

Hospital clinical chemists and their technical aids will welcome this small volume. C. Z.

NEW BOOKS

First Report of Expert Committee on Bilharziasis. WHO Technical Report Series No. 65. Geneva: World Health Organization, 1953 (New York: Columbia University Press, U. S. Agents). Price, $.30.

Cold Injury. Transactions of the Second Conference. Edited by M. IRENÉ FERRER, M.D,. Columbia University. Pp. 242; 86 ills. New York: Josiah Macy, Jr. Foundation, 1954. Price, $4.00.

THIS volume is a report of the Second Conference on Cold Injury and is divided into four sections: (1) The Epidemiology of Cold Injury in Man, (2) Resistance to Cold, (3) Pathophysiology of Cold Injuries and (4) Suggested Areas for Future Discussions and Research. This is a stenographic report of a round-table discussion among investigators active in the field of cold injury. Since there is no effective treatment in frostbite, the epidemiologic approach in the first section is of unusual interest. Here are analyzed in detail the multiple factors: personal, racial, emotional, environmental: which affected the incidence and degree of frostbite among our troops in the Korean war. The last section contains several suggestions for clinical and basic investigation which may provide bait to lure other scientists into the study of cold injury. N. L.

The Jealous Child. BY EDWARD PODOLSKY, M.D. Pp. 147. New York: Philosophical Library, 1954. Price, $3.75.

THE title of this book does it some injustice, since there are 24 additional short chapters dealing with many other problems connected with the emotional growth of children. These include chapters such as "The Psychological Difficulties of the Child with Rheumatic Heart Disease", "The Tuberculous Child's Mental Outlook", "The Step Child", and "The Restricted World of the Diabetic Child". Trying to achieve a happy medium between brevity and inclusiveness the author has given a sound philosophy and helpful suggestions for both the doctor and parent. O. E.

Administrative Medicine; Transactions of the First Conference, Josiah Macy, Jr. Foundation; March 9, 10, and 11, 1953. Edited by GEORGE S. STEVENSON, M.D., Medical Director, National Association for Mental Health. Pp. 176; 6 ills. New York: Josiah Macy, Jr. Foundation, 1953. Price, $3.00.

THIS is an almost verbatim transcript of discussions during a conference which brought together a number of distinguished authorities in various fields concerned with administrative medicine, for the purpose of informally sharing their thoughts on some problems facing medicine today in the effort to utilize our accumulated scientific knowledge in providing for the overall health needs of the individual and the community.

The conference did not attempt to reach any conclusions but this record of the discussions is most interesting and stimulating. The informal style is refreshing. One feels as if he had actually been present at the conference. H. B.

NEW EDITIONS

Quantitative Pharmaceutical Chemistry. BY GLENN L. JENKINS, PH.D., JOHN E. CHRISTIAN, PH.D., and GEORGE P. HAGER, PH.D. 4th ed. Pp. 534; 57 ills. New York: McGraw-Hill Book Co., 1953. Price, $6.50.

THIS is the fourth edition of a work which has been used for 17 years as a textbook for students of pharmacy and as a reference work for analysts. The present edition has, of course, been thoroughly revised and brought up-to-date. It should continue to enjoy wide popularity as a textbook. It is also recommended to anyone who desires an elementary general review of gravimetric and volumetric methods of analysis, special methods of pharmaceutical analysis, and of physicochemical methods. C. Z.